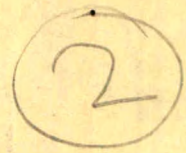
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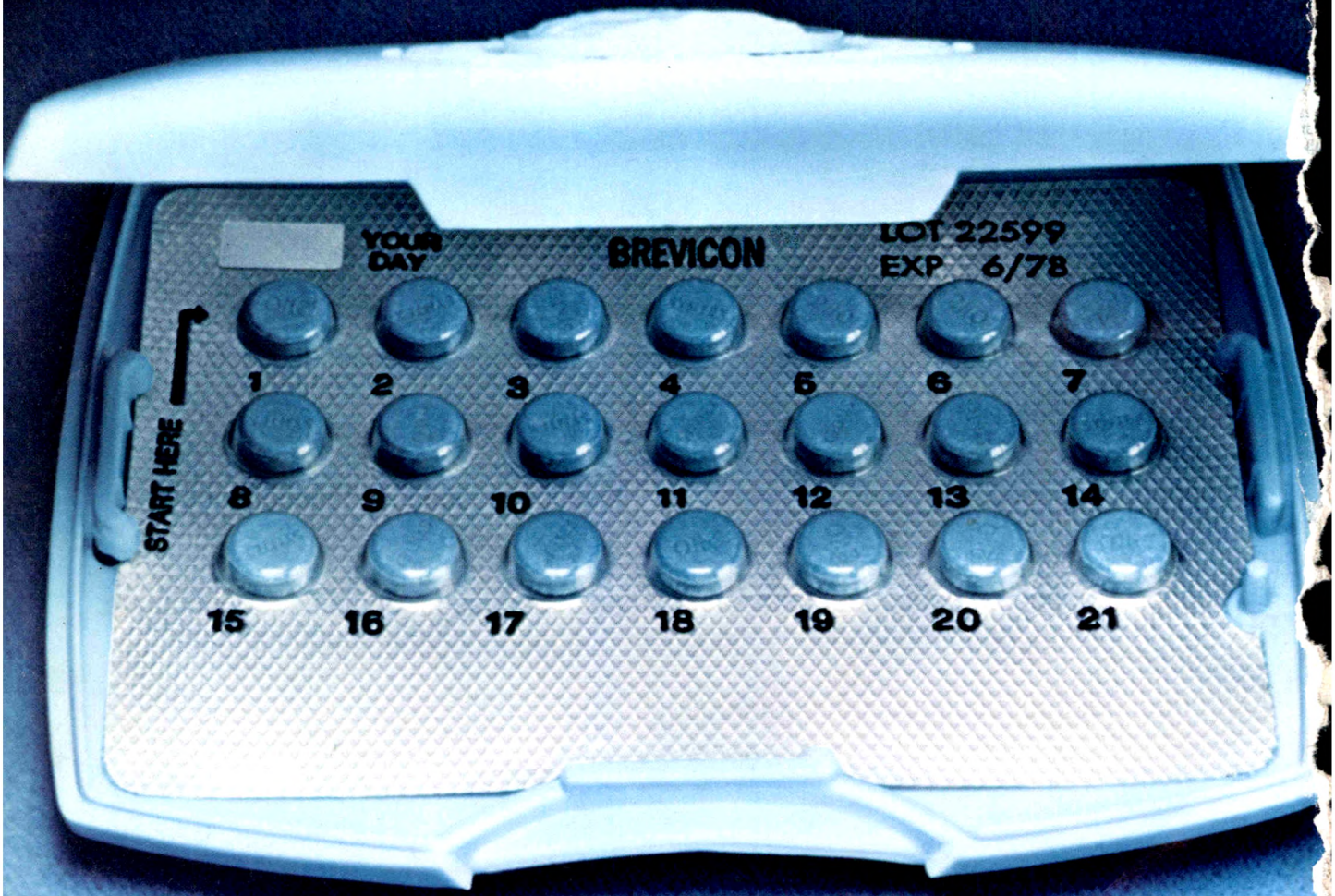


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Effectiveness and low hormonal intake

(2)

(P 24,262

Summary of prescribing information

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with BREVICON®, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

BREVICON tablets are indicated for oral contraception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestation of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

   Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1, 2, 3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of BREVICON tablets in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

5. Hepatic cell adenomas have been reported in women on oral contraceptives. The adenoma may present as an abdominal mass or with the signs and symptoms of an acute abdomen. A bleeding hepatic cell adenoma should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to liver, breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.
2. Endocrine and possibly liver function tests may be affected by treatment with BREVICON tablets. Therefore, if such tests are abnormal in the patient taking BREVICON tablets, it is recommended that they be repeated after the drug has been withdrawn for two months.
3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.
4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.
6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
7. Any possible influence of prolonged BREVICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.
8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving BREVICON therapy.
9. The age of the patient constitutes no absolute limiting factor, although treatment with BREVICON tablets may mask the onset of the climacteric.
10. The pathologist should be advised of BREVICON therapy when relevant specimens are submitted.
11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives:

nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes: tenderness, enlargement and secretion, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by the use of oral contraceptives:

hepatic function: increased sulfobromophthalein retention and other tests, coagulation tests: increase in prothrombin factors VII, VIII, IX and X, thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values, metyrapone test, pregnanediol determination.

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Vitamin B_6 (pyridoxine hydrochloride)	15 mg
Vitamin B_{12} (cyanocobalamin) crystalline	5 mcg
Folic Acid‡	1 mg
Nicotinamide (niacinamide)	15 mg
Vitamin E (*dl*-alpha tocopheryl acetate) (30 mg)	30 IU
Calcium (as calcium carbonate)	350 mg
Magnesium (as magnesium oxide)	1.7 mg
Iodine (as potassium iodide)	0.15 mg
Iron (as ferrous fumarate)	65 mg

Usual dose: One tablet daily

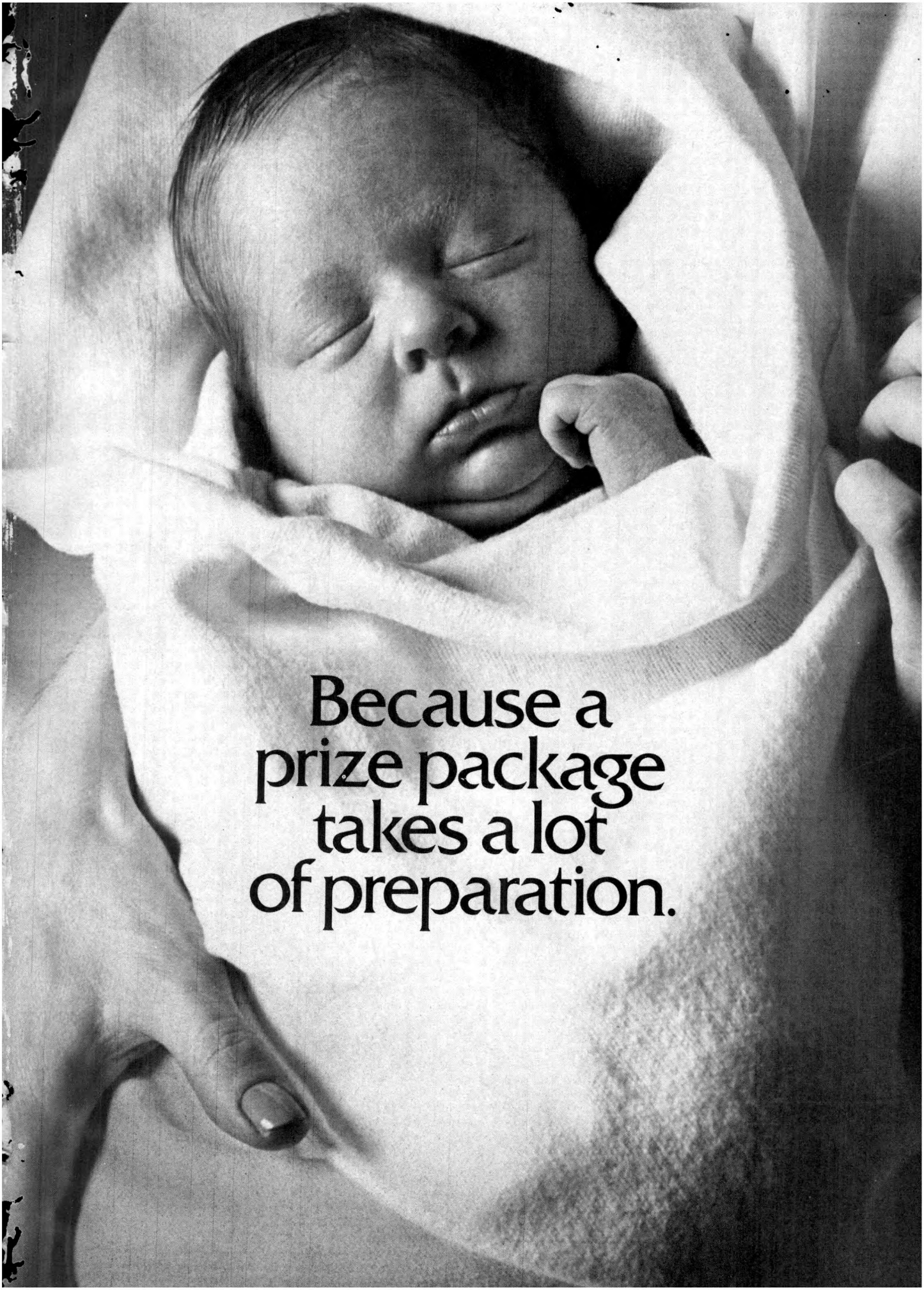
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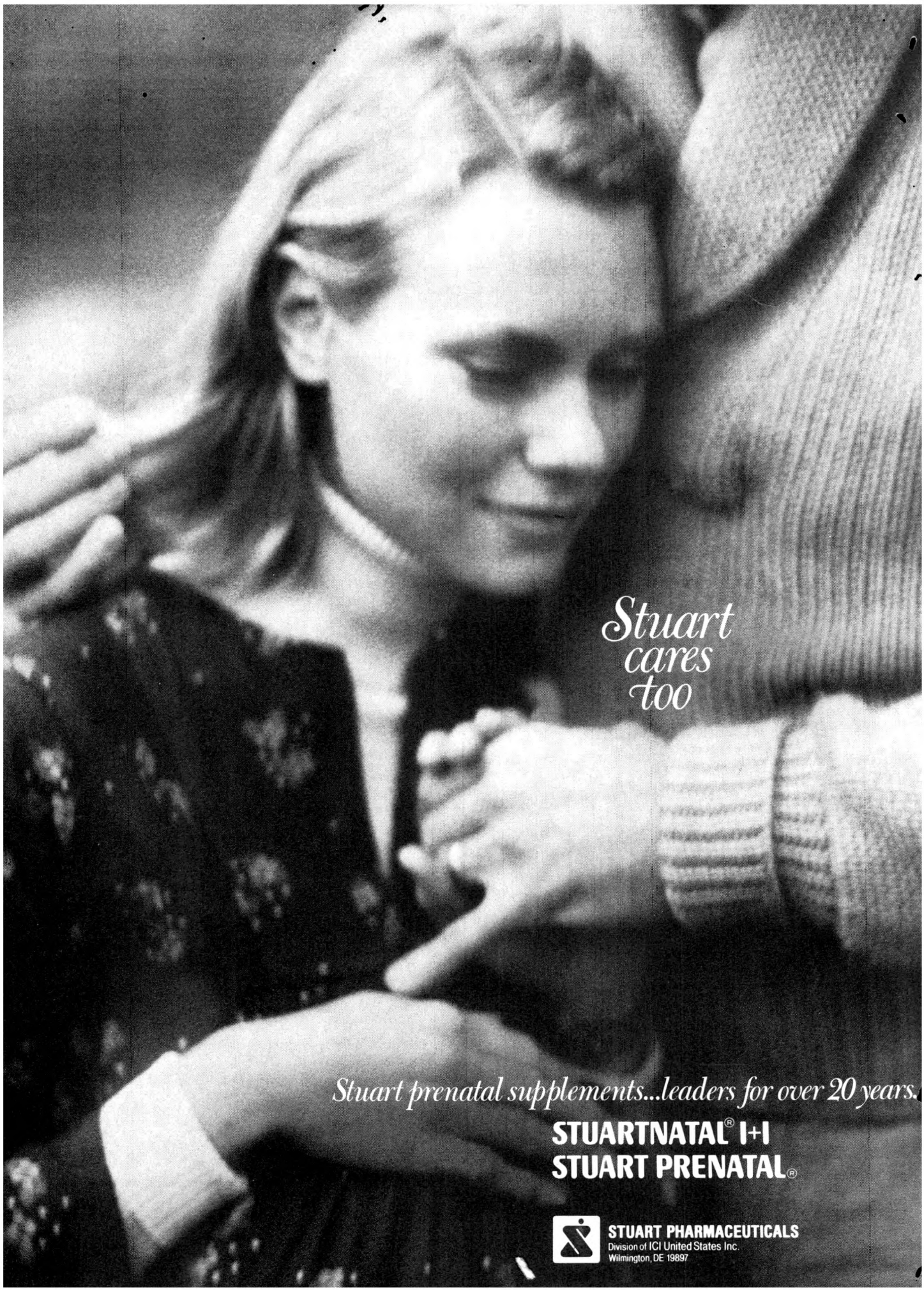
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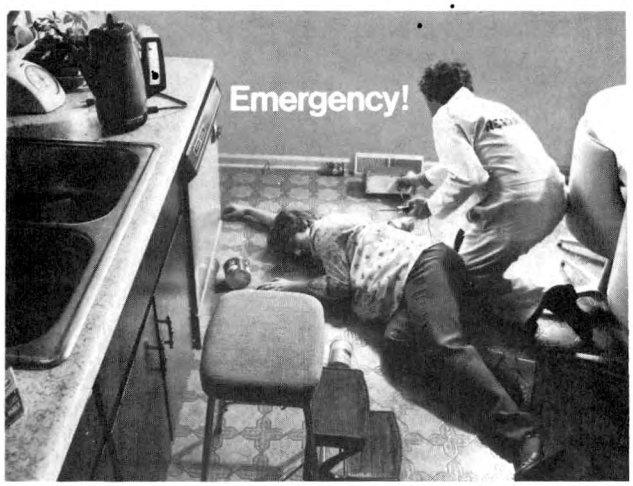
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Robert B. Greenblatt, M.D., C.M., and Virendra B. Mahesh, Ph.D., D.Phil.
Augusta, Georgia

Items

Items 727

(Information for authors on page 21)
(Business communications on page 23)

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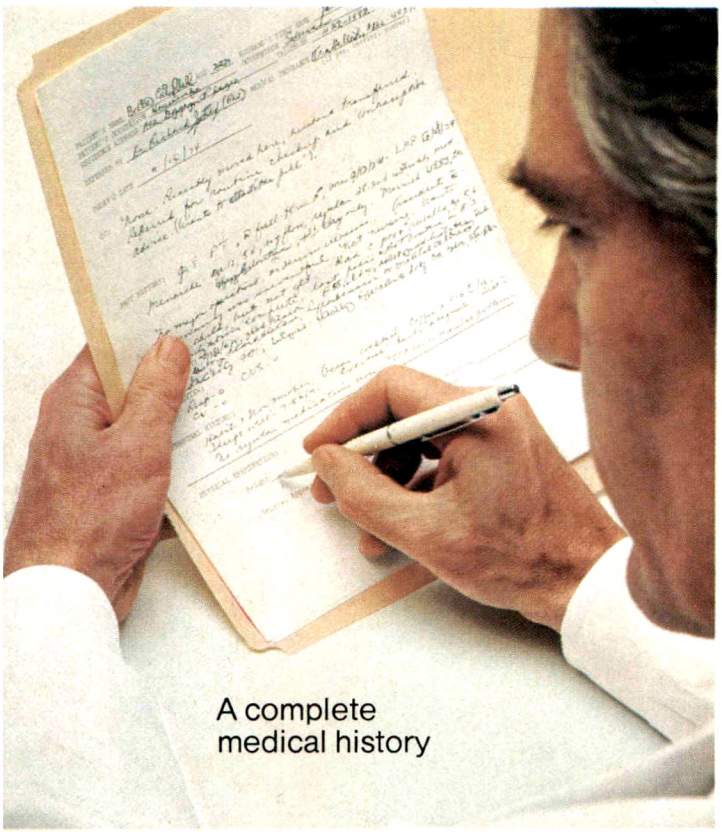
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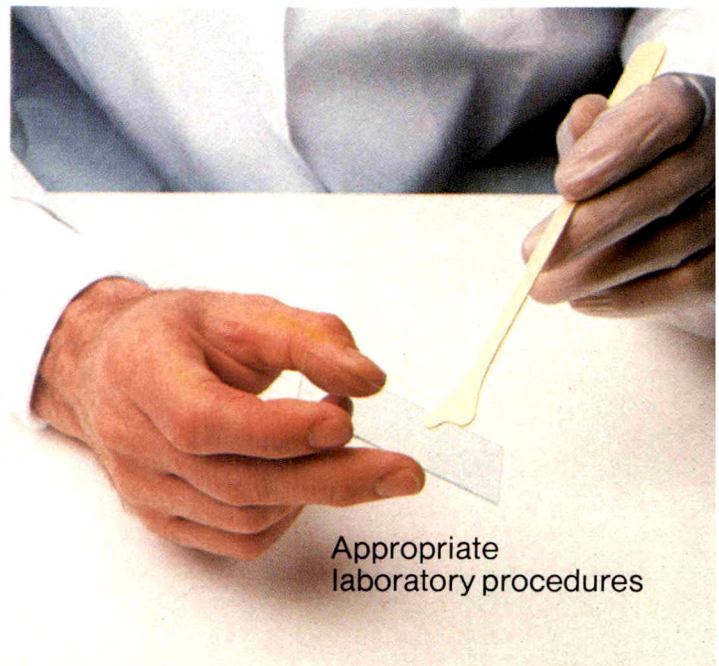
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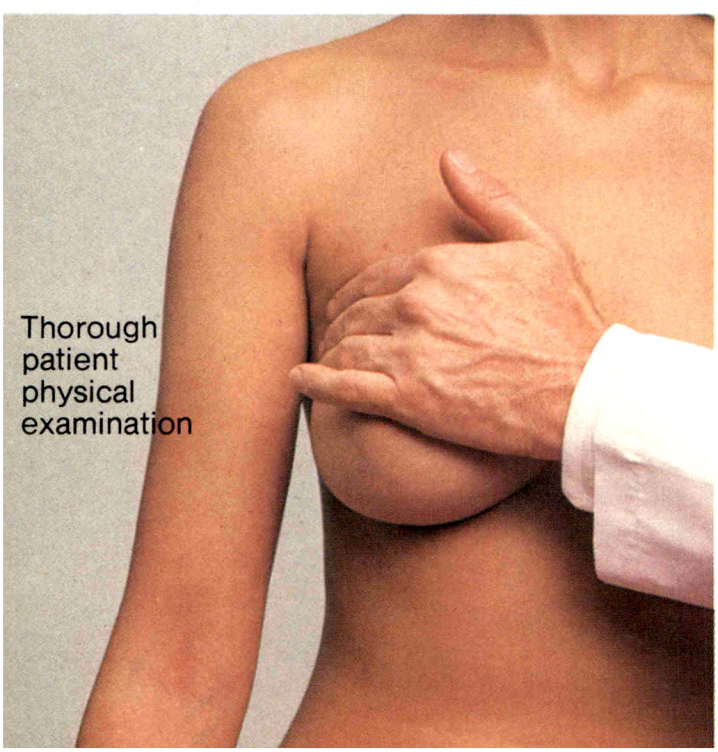
Some sensible steps physicians take before prescribing an oral contraceptive



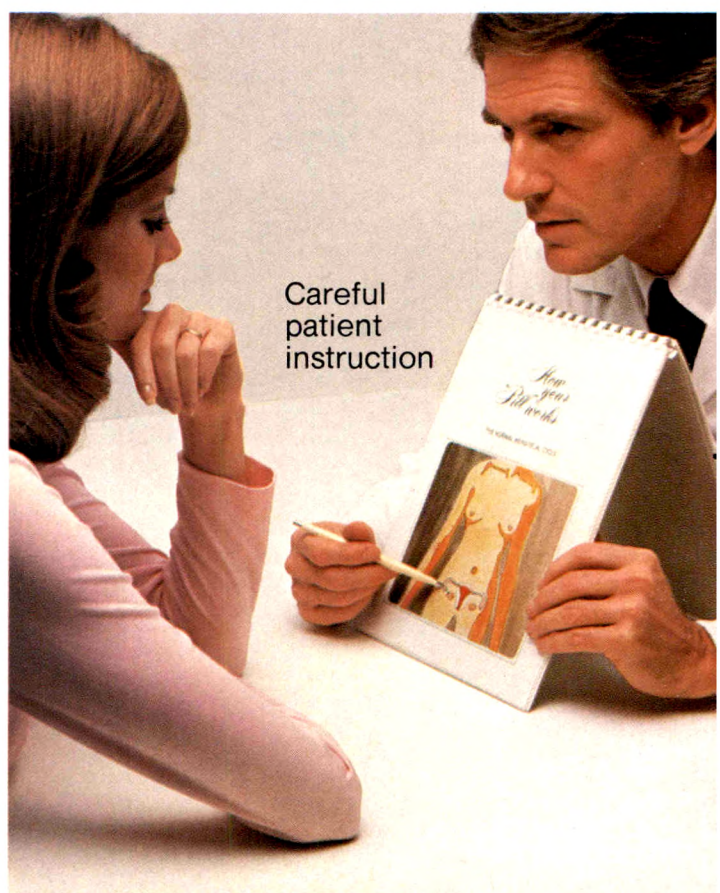
A complete medical history



Appropriate laboratory procedures



Thorough patient physical examination



Careful patient instruction

And when you prescribe a combination oral contraceptive, it's also prudent practice to employ the lowest effective dose of estrogen that is otherwise acceptable.

For many women, this could mean Loestrin 1/20—20 mcg of ethinyl estradiol in combination with 1 mg of norethindrone acetate.

As you would expect, irregular bleeding and occasionally the absence of bleeding, especially during the first few cycles, are more frequent with Loestrin 1/20 than with combinations containing larger doses of estrogen. Nevertheless, clinical trials demonstrated that more than 85% of the subjects, some of whom experienced such irregular cycles, found Loestrin 1/20 an acceptable oral contraceptive.

Effective contraception... with a low dose of estrogen—a tough combination to beat.

The lowest dose of a proven effective estrogen in a combination oral contraceptive

LOESTRIN® 1/20

Each white tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol; each brown tablet contains 75 mg ferrous fumarate, USP.

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See next page for prescribing information.

LOESTRIN 1/20

Each white tablet contains:
norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate) . . . 1 mg
ethinyl estradiol (17 alpha-ethinyl-1,3,5 (10)-estratriene-3, 17 beta-diol) . . . . . 20 mcg
Each brown tablet contains
75 mg ferrous fumarate, USP

BRIEF SUMMARY OF
PRESCRIBING INFORMATION

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of Loestrin 1/20 is somewhat lower than that of the higher-dose combination products. Both provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials that were conducted with Loestrin 1/20, appears to be somewhat higher than observed with higher-dose combination products. This higher dropout rate was observed to be due particularly to irregular bleeding.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

Loestrin 1/20 is indicated for the control of conception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of Loestrin 1/20 in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

2. Endocrine and possibly liver function tests may be affected by treatment with Loestrin 1/20. Therefore, if such tests are abnormal in a patient taking Loestrin 1/20, it is recommended that they be repeated after the drug has been withdrawn for two months.

3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. An alteration in menstrual patterns in many patients is likely to be induced by using Loestrin 1/20. The amount and duration of flow and cycle length may be variable. Because of these irregular bleeding patterns, it is important that the physician take this into consideration when attempting to determine if persistent bleeding is from organic causes.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged Loestrin 1/20 therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Loestrin 1/20 therapy.

9. The age of the patient constitutes no absolute limiting factor, although treatment with Loestrin 1/20 may mask the onset of the climacteric.

10. The pathologist should be advised of Loestrin 1/20 therapy when relevant specimens are submitted.

11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Pulmonary embolism
Cerebral thrombosis

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, e.g. retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea during and after treatment
- Edema
- Chloasma or melasma
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Changes in cervical erosion and cervical secretions
- Suppression of lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (Allergic)
- Rise in blood pressure in susceptible individuals
- Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

- Anovulation post treatment
- Premenstrual-like syndrome
- Changes in libido
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Fatigue
- Backache
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: increased sulfobromophthalein retention and other tests

Coagulation tests: increase in prothrombin, factors VII, VIII, IX, and X.

Thyroid function: increase in PBI and butanol extractable protein-bound iodine, and decrease in T^3 uptake values

Metyrapone test

Pregnanediol determination

DOSAGE AND ADMINISTRATION

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown tablets have been started. Because of the relatively low estrogenic content, Loestrin 1/20 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen to achieve cyclic regularity than that contained in Loestrin 1/20. These patients experience altered bleeding patterns, which do not conform to treatment schedules, while taking the white Loestrin 1/20 tablets. However, it is important that patients adhere to the dosage schedule regardless of when bleeding occurs.

The occurrence of altered bleeding is highest in Cycle 1. The majority of patients will have seven days or less of total bleeding during the 28-day cycle (including both withdrawal bleeding and breakthrough bleeding and spotting). Should irregular bleeding occur, patients should be reassured and instructed to continue taking the tablets as directed. If by the third cycle the irregular patterns are unacceptable, consideration should be given to changing the medication to a product with higher estrogen content (Norlestrin®-1 mg or Norlestrin-2.5 mg). The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic causes, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

SE

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2. Inman W H W and Vessey M P: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. *Br Med J* **2**:193-199, 1968.
3. Vessey M P and Doll R: Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. *Br Med J* **2**:651-657, 1969.
4. Sartwell P E, Masi A T, Arthes F G, Greene G R and Smith H E: Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. *Am J Epidemiol* **90**:365-380, 1969.

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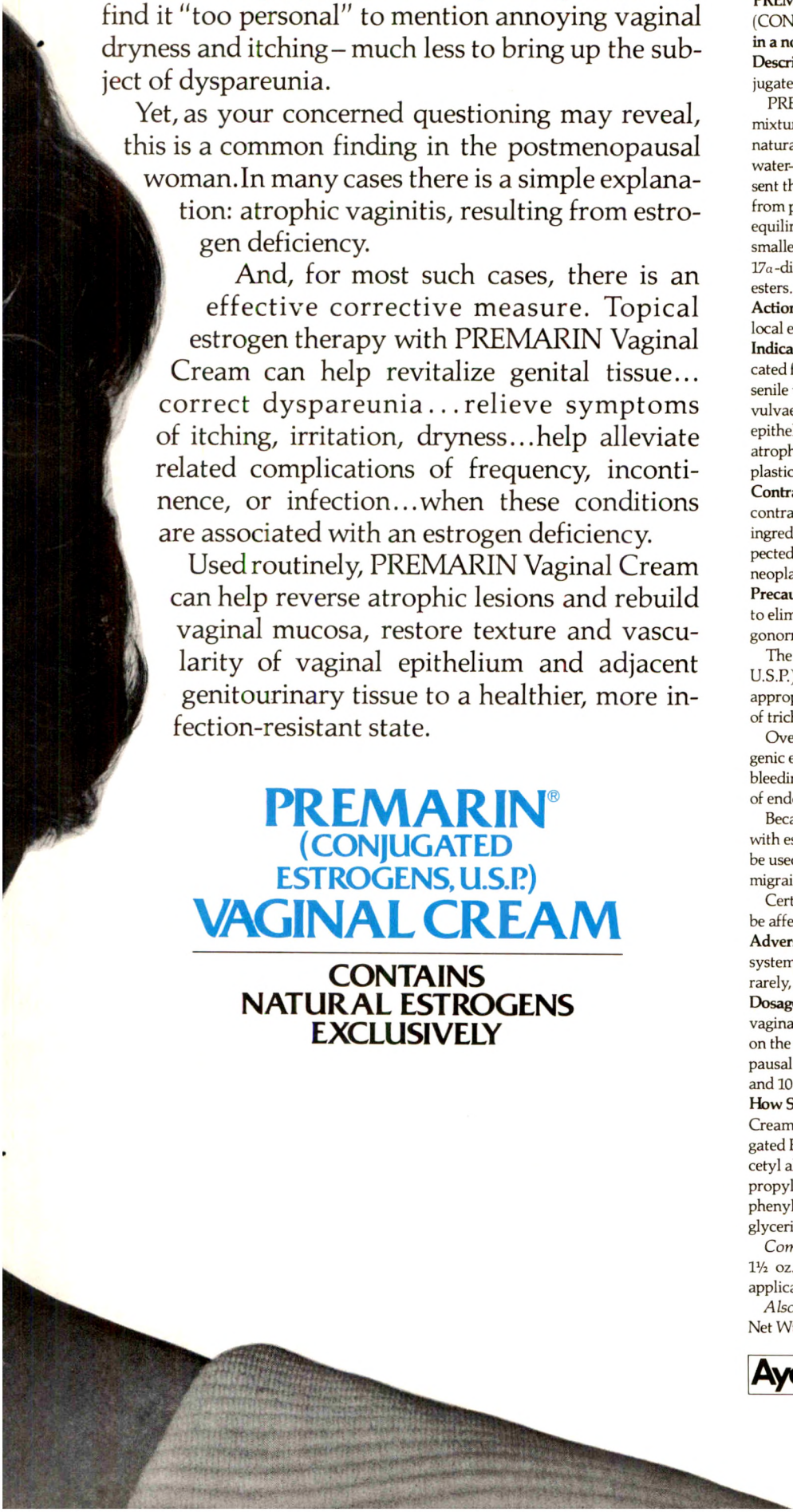
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(Complete text of package circular.)

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in a nonliquefying base

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PREMARIN (Conjugated Estrogens, U.S.P.) is a mixture of estrogens, obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

Actions: PREMARIN Vaginal Cream provides the local estrogenic activity of topical estrogen.

Indications: PREMARIN Vaginal Cream is indicated for the treatment of postmenopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium, dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases.

Contraindications: PREMARIN Vaginal Cream is contraindicated in patients hypersensitive to its ingredients, and in patients with known or suspected cancer of the breast, or estrogen-dependent neoplasia such as endometrial carcinoma.

Precautions: Diagnostic measures should be taken to eliminate the possibility of neoplasia or gonorrhea.

The use of PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream does not preclude the use of appropriate antimicrobial therapy in the presence of trichomonal, monilial, or bacterial infection.

Overdosage may result in systemic hyperestrogenic effects such as abnormal or excessive uterine bleeding, edema, breast tenderness, or reactivation of endometriosis.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

Certain liver and endocrine function tests may be affected by estrogen administration.

Adverse Reactions: Hypersensitivity reactions, systemic effects such as breast tenderness, and, rarely, withdrawal bleeding.

Dosage and Administration: *Usual dosage:* Intravaginally or topically, 2 to 4 Gm. daily, depending on the severity of the condition. In postmenopausal surgery, therapy is suggested 10 days before and 10 days following intervention.

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Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

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†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

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IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

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Assessment of intrauterine growth retardation by diagnostic ultrasound

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In the first 1,000 cases referred to the Department of Diagnostic Ultrasound for Obstetrics and Gynaecology, 200 patients with singleton pregnancies were examined by this modality for possible intrauterine growth retardation (IUGR). Inclusion in this study was based on one or more of the following criteria: past history of IUGR, present clinical impression of IUGR, present high risk of developing IUGR, and unsuspected IUGR evidenced by diagnostic ultrasound. In 34 per cent of cases, serial examinations indicated that the date of confinement had to be recalculated. Ultrasound was in agreement with delivery results in 82 per cent of cases. Sixteen per cent of cases in this study resulted in growth-retarded infants. Ultrasound correctly diagnosed 70 per cent of these.

THE ANTENATAL diagnosis of intrauterine growth retardation (IUGR) continues to frustrate obstetricians. The development of IUGR may be predicted in one half of cases because of past or present obstetric history, or maternal disease complicating the pregnancy. The remaining cases are of idiopathic etiology, and must be detected by the recognition of the fetus who is small for gestational age.[1]

A valuable adjunct to the diagnosis and management of IUGR is fetal assessment by ultrasound cephalometry.

The present study was taken to assess the: (1) accuracy of ultrasound in predicting IUGR, (2) correlation of clinical impression and ultrasound evidence of IUGR, and (3) correlation of predictive risk factors and the development of IUGR.

Materials and methods

The first 1,000 cases referred to the Department of Diagnostic Ultrasound for Obstetrics and Gynaecology at The Toronto Western Hospital were reviewed. Two hundred patients with singleton pregnancies were examined by this modality for possible IUGR.

The equipment used was the Diasonograph NE 4102. The method of scanning was that of combined A and B scan methods as described by Campbell.[4]

From the Department of Diagnostic Ultrasound for Obstetrics and Gynecology, The Toronto Western Hospital.

Presented at the Thirty-first Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, Canada, June 19-22, 1975.

Reprint requests: Dr. John C. G. Whetham, 25 Leonard Ave., Ste. 406, Toronto, Ontario M5T 2R2, Canada.

Table I. Indication for scan

	No. of cases	*Total**
Present diagnosis of IUGR	68	88
Past history of IUGR	4	10
Present high risk for IUGR	50	71
More than one of above	23	
Unsuspected	1	
Total in study	146	

*Includes cases with more than one indication.

Table II. Present high risk for IUGR (71 cases)

	*Total**
Recurrent antepartum hemorrhage	21
Previous stillbirth	10
Rh disease	8
Diabetes	7
Previous C/S	5
Cardiac disease	4
Hypertension	2
Others	14

*Includes cases with more than one indication.

Table III. Recalculation of dates

	Total	*Error*
Present diagnosis of IUGR	28	2
Past history of IUGR	0	0
Present high risk for IUGR	18	0
More than one of above	4	0
Total	50	2

Inclusion in this study was based on one or more of the following criteria: past history of IUGR, present clinical impression of IUGR, present high risk for developing IUGR, and unsuspected IUGR as evidenced by diagnostic ultrasound.

When the biparietal diameter was within normal range, for the menstrual age of the fetus, at the time of the first measurement, then the maturity was assumed to be correct. The growth rate had to be below normal on two successive examinations to put the baby in the "retarded growth" category. If this growth rate was just below the two standard deviations of the mean for that gestational period, then the growth rate was considered borderline.

When the biparietal diameter was below the range for normal menstrual age of the fetus, at the time of the first measurement, then it was considered either that this was due to impaired fetal growth or that the maturity was less than that calculated from the last menstrual period. In a repeat examination, if the growth rate was normal, then it was assumed that the maturity was in error, and the dates were recalculated.[2]

Table IV. Stillbirths (8 cases)

	Total
Present diagnosis of IUGR	4
Past history of IUGR	0
Present high risk for IUGR	2
More than one of above	2

Table V. Over-all results: 146 cases

	Newborn (stillbirth)		
Ultrasound	*Normal*	*Borderline*	*IUGR*
Normal	102	10	6
Borderline	2	2	1
Retarded	1	6	16

The designation of IUGR of the newborn infant was given if this diagnosis was made, or if a stillbirth occurred and the weight was below the tenth percentile for that gestational period. If the birth weight was below the tenth percentile, but the newborn infant was not described as growth retarded, then the case was assigned to the borderline category.

The average interval between examinations was 2 weeks. Patients with a previous history of IUGR or present risk for IUGR were usually referred in the second trimester for the first scan. When a present diagnosis of IUGR was present, these patients were referred for their initial scan usually in the third trimester.

Analysis of data

Of the 200 cases reviewed, 146 had sufficient delivery data to be included in this study. The indications for inclusion in this study are shown in Table I. Twenty-three cases had two or more indications for possible IUGR.

Table II shows the indications for high risk for IUGR, excluding those cases with a past history of delivery of an IUGR infant.

The biparietal growth chart used was that of Campbell.

Fifty cases met the requirements for recalculation of dates as shown in Table III. In two of the cases, this recalculation was thought to be in error, and will be discussed later.

Sixty-eight per cent of the patients were delivered vaginally, 29 per cent had primary cesarean sections, and 3 per cent had repeat cesarean section.

The stillbirths in this series are shown in Table IV. The rate was 5.5 per cent. These will be discussed in detail.

The over-all results are shown in Table V. There were 105 infants considered normal at birth (no evidence of IUGR), 18 cases were borderline, and 23 were small for gestational age.

The biparietal measurements were retarded in 23 cases, borderline in five, and normal in 118. The agreement between ultrasound and classification at birth was 82 per cent. Ultrasound predicted 70 per cent of the IUGR cases.

Table VI shows the results when the indication for study was the impression of a growth-retarded fetus. Fifteen per cent of infants in this category were growth retarded. Ultrasound predicted 62 per cent of these infants.

When the indication was a present high risk for IUGR (Table VII), excluding past history of IUGR, 17 per cent of these infants were growth retarded. Ultrasound predicted 83 per cent of these infants.

When there was a past history of IUGR, 30 per cent of these infants were growth retarded at birth, and ultrasound predicted all of them. When more than one

When there was a past history of IUGR, 30 per cent of these infants were growth retarded at birth, and ultrasound predicted all of them. When more than one indication was given, 30 per cent of these infants were growth retarded, and ultrasound predicted 86 per cent.

One patient was scanned because the size was felt to be greater than the dates. Ultrasound was correct in predicting a growth-retarded infant.

Table VI. Present diagnosis of IUGR: 88 cases

	Newborn (stillbirth)		
Ultrasound	*Normal*	*Borderline*	*IUGR*
Normal	62	9	4
Borderline	0	1	1
Retarded	1	2	8

Table VII. Present high risk for IUGR: 71 cases

	Newborn (stillbirth)		
Ultrasound	*Normal*	*Borderline*	*IUGR*
Normal	50	1	2
Borderline	2	2	0
Retarded	0	4	10

Table VIII. Predictive risk factor

	IUGR(%)
Past history of IUGR	30
More than one indication	30
High risk for IUGR	17
Clinical impression of IUGR	15
Over all	16

Comment

Sixteen per cent in this study resulted in growth-retarded infants. A further 12 per cent were borderline by birth weight. The two most significant indicators appear to be a past history of IUGR (30 per cent) and when more than one indication is present (30 per cent) (Table VIII).

Ultrasound is valuable in differentiating between mistaken menstrual age and possible growth retardation. Recalculation of dates in the former avoids possible premature delivery of an otherwise normal infant. In this study, recalculation was considered correct in all but two. In each of these two cases, growth was acceptable on two successive examinations. One patient, with recalculated dates (back 4 weeks) delivered, at 38 weeks, a dysmature female infant weighing 2,690 grams. The second patient was initially scanned for possible microcephaly. Growth was good and dates were recalculated (back 8 weeks). Fetal death occurred by the third examination, and the patient delivered a stillborn female infant weighing 2,855 mg. at 31½ weeks (recalculated). In this latter situation, the obstetrician described the results as confusing. We have no explanation for this, since there was no evidence of microcephaly at delivery.

Ultrasound failed to predict IUGR in four of 13 cases with the present suspicion of IUGR (31 per cent). Two of these cases are described above, and their dates were recalculated. A further two showed good growth and consistent with menstrual data. One patient was last scanned 6 weeks prior to intrauterine death and a stillborn female infant weighing 2,430 grams was delivered at 39 weeks. The other patient was probably scanned too late, at 39 and 41 weeks by dates. At 42 weeks she delivered a dysmature female weighing 2,495 grams.

A fifth patient, who delivered a growth-retarded female infant weighing 1,810 grams at 33 weeks, was considered to have borderline growth on ultrasound. Amniotic fluid studies, including bilirubin, creatinine, L/S ratio, and fat cells, agreed with the borderline maturity of the ultrasound.

In one case, with the suspicion of IUGR, ultrasound predicted a growth-retarded infant. This patient delivered a healthy male infant weighing 3,250 grams at 42 weeks. This patient failed to return for additional scans. The two scans performed at 32 and 35 weeks were both below the expected size for that gestational age. However, growth was greater than expected, and

for that reason recalculation of dates was not made. In retrospect, further scans may have justified recalculation and avoided this overcall.

There were six cases in which ultrasound predicted IUGR. At delivery all infants were below the tenth percentile for weight, but were not described as growth retarded. Campbell and Kurjak[3] explained this by suggesting that the biparietal growth may slow at a time when the baby is still above the fifth percentile for weight. This would explain four of these cases.

Ultrasound failed to diagnose IUGR in two patients in the high-risk category. One patient with dermatomyositis was on prednisone. Despite good growth on four serial scans, the patient delivered a dysmature male infant weighing 2,340 grams at 37 weeks.

The second patient was a 41-year-old grandmultipara, who was diabetic and had had two recent myocardial infarctions. A total of seven biparietal measurements were performed with good growth until the last two visits. The last two values fell within the two standard deviations of the mean for the gestational periods. The patient's diabetes was poorly controlled and she refused to stay in hospital. Sixteen days following her release from hospital, she returned with an intrauterine death at 34 weeks. At 37 weeks she delivered a stillborn male weighing 1,740 grams.

One stillbirth (unexplained) occurred in a patient who had been scanned for possible intrauterine growth retardation. Serial scan showed good biparietal growth. The last scan was performed 6 weeks prior to intrauterine death.

The remaining five stillbirths were related to Rh disease (2), prolapsed cord at 29 weeks (1), and unexplained (2). Ultrasound biparietal diameter growth was severely retarded in all of these.

In the category of present diagnosis of IUGR 17 patients are included who had only one ultrasound examination. In all these, examinations were performed between 20 and 28 weeks and the biparietal diameters were within the normal range for menstrual ages of the fetuses. It has been our policy that, if the above situation exists, with early scanning, and to avoid excessive repeat examinations, the patient is returned to her physician with the suggestion of rebooking if the physician so desires. There was no evidence of intrauterine growth retardation in any of these cases.

Scanning of patients at risk of IUGR or with a past history of IUGR should ideally begin between 20 and 26 weeks with serial follow-up at 2 to 4 week intervals. In such cases where a diagnosis of IUGR is made, serial scans should be made every 2 weeks until delivery. When the clinician diagnoses possible IUGR, scanning should commence as soon as possible and, where indicated, continue at 2 week intervals.

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The value of prophylactic antibiotics after vaginal hysterectomy

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Prophylactic antibiotics were given postoperatively to a consecutive series of 74 patients who underwent vaginal hysterectomy. Antibiotics were administered in the immediate postoperative period. There was a highly significant decrease in febrile morbidity in the treated group compared to 190 control subjects having similar surgery but treated with antibiotics only on the appearance of fever and/or other signs of infection. There was a failure to relate the increased febrile morbidity in the control group to patient's age, menopausal state, type of catheterization, or to the type of operative procedure. The increased morbidity in the control group related only to the failure to use prophylactic antibiotics. The antibiotic-treated portion (58 per cent) of the control group had a longer period of hospitalization.

IN THIS ARTICLE, febrile morbidity is defined as a temperature of 38.0° C. (100.4° F.) or higher, occurring on any 2 separate postoperative days excluding the first 24 hours.

It is common knowledge that febrile morbidity is higher after vaginal hysterectomy than after other gynecologic operations. Many factors have been suggested as the cause of this increased morbidity,[1–3] such as patient's age, social group, preoperative vaginal preparation, operative blood loss, operative techniques, associated repair, and the surgeon's lack of experience. There is still no universal agreement about the relative contributions of these factors. Perhaps the most important factor is that the vagina is an unsterile field which cannot be properly sterilized preoperatively. It would not be unexpected, therefore, for vaginal hysterectomy to result in infection of both the vault of vagina and the pelvic peritoneum.

The use of antibiotics to combat this problem can be considered under three different approaches: (1) administration only in the presence of evident infection, a practice followed by probably the majority of gynecologists; (2) prophylactic administration starting before and continuing after operation; several authors[3–5] have shown a significant reduction in the incidence of febrile morbidity with this regimen; (3) prophylactic antibiotics given only after operation, as was done in the present study.

Our inquiry was concerned principally with the following questions: (1) which of the three approaches, described above, provides the lowest incidence of postoperative febrile morbidity? (2) Does a decrease in febrile morbidity affect the duration of hospital stay? (3) Does the delay in the use of antibiotics affect the duration of hospital stay? (4) Does the use of prophylactic antibiotics increase the total antibiotic usage? (5) Are there other factors which affect febrile morbidity?

Presented at the Thirty-first Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, Canada, June 19-22, 1975.

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Patients and methods

All patients studied had been admitted to the Gynaecology Service of the Queen Elizabeth Hospital, Montreal, between January 1, 1969, and January 1, 1974. On admission, all patients underwent a complete medical and physical examination. Routine laboratory studies, including hemoglobin, white blood cell count, urinalysis, and chest x-ray, were done. Routine cultures of the vagina, to determine antibiotic sensitivity, were not done. No vaginal douching or insertion of antibiotic suppositories into the vagina was done on the ward. All patients (74) admitted to the service of one of us (M. E. B.) and undergoing vaginal hysterectomy were included in the treated group (Group A). They were treated postoperatively with ampicillin, 500 mg., four days a day, for 5 days; on the first postoperative day the antibiotic was given intravenously and thereafter it was given orally The first dose was given on admission to

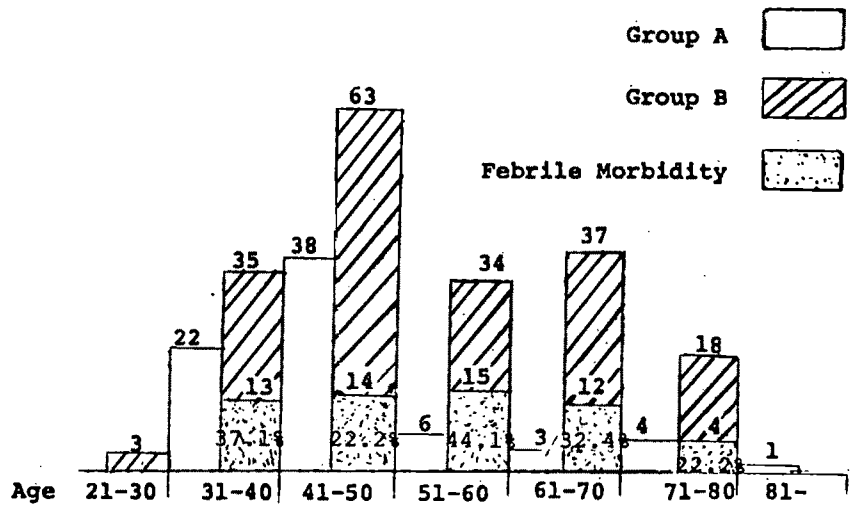


Fig. 1. Age, distribution, and febrile morbidity.

the recovery ward. At the end of day 5, antibiotics were discontinued unless there was some indication for their continued usage or substitution, e.g., urinary antibiotics for a persistent bacteriuria or cystitis.

Group B consisted of 190 patients who were admitted concurrently to the same service by other members of the gynecologic staff, and who also had vaginal hysterectomy. These patients were given antibiotics only for specific indications, in which case the antibiotics were usually started on the third or fourth postoperative day. The usual indication in this group was the onset of fever, development of a cuff abscess, or urinary tract infection.

The age distribution of the two groups is shown in Fig. 1. The average age in Group A was 46.4 years (range, 33 to 82); in Group B it was 52.0 (range 26 to 79). Whereas 89 (47 per cent) of Group B patients were over 50 years of age, only 19 per cent (14 patients) were so in Group A. In Group A, 57 of the 74 patients were premenopausal; 16 had suprapubic and 58 urethral catheterization. In Group B, 102 of the 190 were premenopausal, 29 had suprapubic and 161 urethral catheterisations performed. Further details are given under Results. Operative technique was similar but not identical in the two groups of patients. In particular, in Group A, posterior repairs were limited to extensive dissection of enterocele sacs with excision of lax posterior and superior vaginal mucosa; this modified posterior repair was done in only 45 per cent of Group A patients. In contrast, 64 per cent of Group B patients has classical posterior repairs. In Group A, extensive use was made of hemostatic sutures which encircled the vaginal cuff approximating the vaginal mucosa and perineum. This was not the case in Group B.

The bladder was catherized postoperatively in all patients in both groups. In Group A, however, more extensive use was made of a suprapubic Foley catheter inserted with the aid of a perforated uterine sound.

The patient's oral temperature was normally taken at 07:00, 11:00, 15:00, and 19:00 hours each day. If fever was noted, the temperature was then taken every 6 hours until the patient was afebrile.

Results

Febrile morbidity in Group A was limited to two patients (2.7 per cent). One was an 82-year-old woman with procidentia and urinary incontinence to a degree that commitment to a nursing home was anticipated. Postoperatively she developed pulmonary atelectasis and a hospital stay of 13 days was required before she was discharged home, continent. The second patient had a vaginal hysterectomy with anterior repair at the age of 49. Urethral drainage was used. She had fever on two separate occasions but was able to leave hospital on the sixth day.

In contrast, 61 of 190 patients in Group B showed febrile morbidity, an incidence of 32.1 per cent of the group and a highly significant number ($P < 0.001$).

The distribution of febrile morbidity in relation to age is shown in Fig. 1. It shows that febrile morbidity occurred in all age groups of Group B patients.

The menopausal states as it relates to febrile morbidity was as follows: of the 190 patients in Group B, 102 (54 per cent) were premenopausal and 29 (28.4 per cent) of these had febrile morbidity; of the 88 postmenopausal patients (46 per cent of Group B), 28 had febrile morbidity, an incidence of 31.8 per cent. The menopausal state therefore had no significant

Table I. Type of postoperative catheterization and febrile morbidity

	Group A		*Group B*			
					Febrile morbidity	
	No.	*%*	*No.*	*%*	*No.*	*%*
Suprapubic	16*	22	29	15	8	27.6
Urethral	58*	78	161	85	50	31.1
Total	74	100	190	100		

*One patient in this group showed febrile morbidity.

Table II. Type of operation and febrile morbidity

	Group A		*Group B*			
					Febrile morbidity	
	No.	*%*	*No.*	*%*	*No.*	*%*
Vaginal hysterectomy only	24	32	24	13	7	29.2
Vaginal hysterectomy and anterior repair	14*	19	43	23	16	37.2
Vaginal hysterectomy and posterior repair	3	4	2	1	—	—
Vaginal hysterectomy and anterior and posterior repair	33*	45	121	64	35	28.9
Total	74	100	190	100		

*One patient in this group showed febrile morbidity.

Table III. Hospital stay and febrile morbidity

	Group A (74 cases)	*Group B (190 cases)*
Average hospital stay (days)	7.5	8.7
Febrile morbidity (no. of cases)	2	61
Febrile morbidity (% of cases)	2.7	32.1

Table IV. Antibiotic usage, hospital stay, and febrile morbidity

	Group A	*Group B*
I. Antibiotics not used:		
Cases	—	79 (42%)
Average duration of hospital stay (days)	—	7.3
Febrile morbidity	—	9 (11.4%)
II. Antibiotics used:		
Cases	74 (100%)	111 (58%)
Average number of days on antibiotics	5.2	5.6
Average duration of hospital stay (days)	7.5	9.7
Incidence of febrile morbidity	2 (2.7%)	52 (46.8%)

effect on febrile morbidity in patients of Group B.

Table I gives the data for the type of bladder catheterization, 18 (27.6 per cent) had febrile morbid- were employed: suprapubic or urethral. In Group A, only two patients had febrile morbidity. One had urethral catheterization and the other had suprapubic catheterization. In Group B, where 29 had suprapubic catheterization, 18 (27.6 per cent) had febrile morbidity; of the much larger number (161) with urethral catheterization, 50 (31.1 per cent) had febrile morbidity. Here too, therefore, the type of catheterisation procedure employed had no apparent different effect on the incidence of febrile morbidity in patients not receiving prophylactic antibiotics.

The relationship of the type of operative procedure preferred to the incidence of febrile morbidity is detailed in Table II. While the numbers of cases in each of the four types of operation performed were very uneven, no striking differences were apparent. The figures for the incidence of febrile morbidity (29.2 per cent) in 24 patients having a vaginal hysterectomy alone, and the 28.9 per cent in the 121 having vaginal hysterectomy combined with anterior and posterior repair were almost identical. Despite the large difference in the size of the two groups (24 vs. 121 cases), it is of clinical interest that the more complicated type of operation which also had the larger number of patients had no higher incidence of febrile morbidity.

The over-all incidence of febrile morbidity was examined in terms of duration of hospital stay in both groups. Table III shows that patients in Group B stayed in hospital 8.7 days in contrast to 7.5 days in Group A. Statistically this difference is not significant ($p > 0.5$).

Table IV shows the results of antibiotic treatment on hospital stay and febrile morbidity. In part I of Table IV we see that 42 per cent of Group B patients did not have any antibiotics. Their hospital stay was almost identical to the over-all hospital stay of Group A, viz., 7.3 vs. 7.5 days. Febrile morbidity occurred in 11.4 per cent of this portion of Group B.

In part II of Table IV the average duration of hospital stay and the incidence of febrile morbidity are compared with the 58 per cent of Group B who were placed on antibiotics in the postoperative period and all of Group A who received antibiotics prophylactically.

The average number of days each group received antibiotics was very similar. While there was a considerable difference in the average duration of hospital stay, viz., 7.5 days for Group A and 9.7 days for Group B, this difference was not statistically significant ($0.3 < p < 0.4$). Group B patients who received antibiotics spent an average of 2.2 days longer in hospital. Febrile morbidity occurred in 46.8 per cent of this portion of Group B cases. This shows that reasons other than febrile morbidity, as we have defined it, accounted for 53.2 per cent of antibiotic usage in this group. Reasons included bacteriuria, cystitus, purulent vaginal discharge, and fever, which did not meet our criteria for febrile morbidity.

Comment

The lesson of the fifties was that the widespread use of antibiotics, and in particular their prophylactic use, was not only useless in preventing wound infection, but positively dangerous in the way it encouraged the development of antibiotic-resistant organisms. More recent studies have also demonstrated the harm that can result from the unrestricted use of antibiotics. For example, in a recent report from Scotland,[4] following the prophylactic use of antibiotics on a neurosurgical ward, not only was there failure to demonstrate a decreased rate of wound infection but virulent Klebsiella infections soon developed which disappeared only when the routine use of antibiotics was markedly decreased.

We feel that the above dictum will have to be re-evaluated with regard to the use of antibiotics in conjunction with vaginal hysterectomies. Gynecologic surgery performed through the unsterile vagina into the peritoneal cavity is not comparable to general surgery done through the almost completely sterile skin into the same cavity. In operations such as herniotomy, simple ovarian cystectomy, and craniotomy, the incidence of wound infection is so very low that one would be hard pressed in these situations to justify the use of prophylactic antibiotics. Besides the quantitative difference in infections after vaginal hysterectomy, there is a marked qualitative difference. Surgical wounds of the abdomen often cause little increase in the patient's morbidity or duration of hospital stay; in contrast, pelvic infections with vault or tubo-ovarian abscess increase both hospital stay and morbidity and cause occasional deaths.

Since the bacteriology of the vagina is almost identical to that of the colon and because the vagina cannot be effectively sterilized, a more reasonable comparison would be to the opening of the unprepared colon at the time of laparotomy with its subsequent contamination of the peritoneal cavity. It is of interest that in cases of this sort (opening of the unprepared bowel), the use of prophylactic antibiotics can reduce the incidence of wound infections from 30 to 8 per cent.[5] The final figure (8 per cent) is similar to those which have been reported with the use of prophylactic antibiotics in conjunction with vaginal hysterectomy in this study.[2, 3, 6]

Our mode of usage of the antibiotics requires some comment. In all published series[2, 3, 6] the antibiotics were given prior to surgery as well as during the postoperative course. We did not feel that preoperative antibiotics were necessary and omitted them. The results we obtained were superior to those where the preoperative dose was given. Goosenberg and associates[2] found a 9.8 per cent febrile morbidity rate in their patients with prophylactic antibiotics were used. Allen and associates[6] reduced their morbidity rate to 14 from 40 per cent in control groups. The elimination of the preoperative dose also saved the resident and nursing staff much effort. It also saved us the necessity of predicting when the patient would come to the operating room so that the preoperative dose could be given 2 hours before surgery started.

The reduction of febrile morbidity when prophylactic antibiotics are used is highly significant, i.e., from 32.1 per cent in the control group to 2.7 per cent in the study group. An incidence of 32.1 per cent febrile morbidity in the control group is similar to large series of vaginal hysterectomies where prophylactic antibiotics were not used. For example, Hawksworth and Roux[7] found that 32 per cent of their patients showed febrile morbidity and Goosenberg's control group had a febrile morbidity of 77.5 per cent. The figures themselves are perhaps less striking than visualization of the temperature charts themselves. The contrast between the rather hectic febrile charts seen in the control group and the almost monotonously flat temperature chart in the study group is most impressive. Besides adding greatly to the patient's comfort, the ease of her convalescence, and the lessening of nursing care required, reduction of febrile morbidity decreases hospital stay. The 190 patients in the control group spent an average of 1.2 extra days in hospital. At the Queen Elizabeth Hospital of Montreal, a ward bed cost $91.00 a day, as of January 1, 1974. Since there were 190 patients in this group, a potential saving of $20,748.00 might have been realized ($190 \times 91 \times 1.2$) by a similar reduction in febrile morbidity.

The usual method of prescribing antibiotics to postoperative patients is to await the development of fever before using them. In the control group this was the usual reason for starting therapy. The result of this

delay is a prolongation of hospital stay. In 58 per cent of the patients, it was felt necessary to start antibiotics in the postoperative period and this group of patients had an average of 9.7 days in hospital—2.2 days longer than the study group. Ledger and associates[8] found that 43.4 per cent of all their patients who had a vaginal hysterectomy were given antibiotics in the postoperative period. It appears that approximately 50 per cent of patients who have a vaginal hysterectomy will require antibiotics in the postoperative period. The delay in commencing therapy appears to allow infection to become well established in the peritoneal cavity and vault, thus making its eradication much more difficult and more time-consuming.

The use of prophylactic antibiotics does increase the total antibiotic usage on a gynecologic floor. The control group stayed on antibiotics a slightly longer average time than the study group (5.6 days in contrast to 5.2 days), the total number of patient days on antibiotics being 111 × 5.6 or 621.6 patient days. If all the 190 patients in the control group had been placed on antibiotics, and assuming a similar result as was obtained in the study group, then (190 × 5.2) or 988 patient days of therapy with antibiotics would have been required. This would represent a theoretical increase of 58.9 per cent in antibiotic usage.

No development of antibiotic-resistant strains was found in either the control or study group. One patient in the study group was allergic to penicillin, and erythromycin was substituted for ampicillin.

Because only two of the patients in the study Group A showed febrile morbidity, it is difficult to relate the importance of the patient's age, menopausal state, or the extent of the surgical procedure to the morbidity which developed. This is in contrast to the work of Pratt and Galloway[9] and of Chehab,[10] who related morbidity to patient's age and operative technique, respectively.

We feel that the development of hematomas in an infected field like the vagina is almost certain to result in vault infections. Meticulous hemostasis is necessary to prevent the formation of hematomas and we think that this is not possible without interrupted sutures which include both vaginal mucosa and pelvic peritoneum and which encircle the vault.

The limited use of the classic posterior repair is also noted in the study group. We believe that this part of the operation is, for the most part, unnecessary, and that the extensive tissue dissection adds to the morbidity and discomfort in the immediate postoperative course, and may cause dyspareunia in the remote postoperative period.

Suprapublic catheterization falls into a similar category. It is difficult to show that it contributes to decreased febrile morbidity, but it does facilitate the postoperative care and comfort of these patients. As shown in the tables, the morbidity of Group B remained consistent, whether urethral or suprapubic catheter was used (Table I), despite the type of surgery (Table II) or the age of the patient (Fig. 1.).

Because of the decreased febrile morbidity, increased patient comfort, and shortened hospital stay, the use of prophylactic antibiotics with gynecologic operations is now more a question of when they should be used, the dosage, and for what period of time, rather than whether they should be used at all. We think they are advisable with all vaginal hysterectomies, that it is not necessary to give them before surgery, and that high doses immediately after surgery are sufficient.

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Amniotic fluid tests for fetal maturity in normal and abnormal pregnancies

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Amniotic fluid creatinine, percentage of lipid-positive cells, and L/S ratio were determined on 285 samples from normal pregnancies and 222 samples from abnormal pregnancy states (Rh isoimmunization, diabetes, hypertensive disorders, intrauterine growth retardation, and hydramnios). In normal pregnancy the coefficient of correlation between true gestational age and estimated period of gestation (EPG) based on the three parameters was 0.94, in Rh isoimmunization 0.77, in diabetes 0.67, and in hypertensive disorders 0.59. In intrauterine growth retardation both the L/S ratio and creatinine were depressed, the coefficient was 0.61, and the EPG was consistently less than the true gestational age. The mean L/S ratio in pre-eclampsia was slightly below the normal mean and in diabetes the mean L/S ratio was also depressed. In 150 samples taken within 48 hours of delivery L/S ratios were accurate in assessing fetal pulmonary maturity although there was a 20 per cent incidence over all of false-immature values. There were no false-mature values except in diabetes (2/9).

IN A PREVIOUS paper, entitled "Amniotic fluid tests for fetal maturity," Doran and associates[1] studied 17 biochemical parameters and one cytologic test (per cent of lipid-positive cells) in amniotic fluid. Of these, the three best tests for fetal maturity were percentage of lipid-positive cells, lecithin/sphingomyelin ratio, and creatinine. By utilizing a graph containing the mean values of the three parameters, the estimated period of gestation (EPG) was produced, which had a correlation coefficient of 0.95 when compared with the actual period of gestation. This method of assessment was found to be more accurate than that resulting from the estimation of any single parameter. A total of 250 samples of amniotic fluid were studied but there were insufficient abnormal pregnancy fluids present (51) to permit statistical analysis of any difference between the two groups. The crucial question is whether amniotic fluid tests for fetal maturity continue to be of value in the abnormal pregnancy states where intervention is often required. In this study, in a larger series, we have compared the accuracy of these tests in normal pregnancy against abnormal pregnancy states (i.e., diabetes, Rh isoimmunization, intrauterine growth retardation, hydramnios, and hypertensive disorders).

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Material and methods

A total of 508 amniotic fluid samples were obtained from 360 patients. Only patients of known gestation were included in the study. Sources of amniotic fluid were as follows: amniocentesis for Rh isoimmunization (100 samples), amniocentesis for maturity (187 samples), fluids collected at cesarean section (79 samples), fluids collected at amniotomy (39 samples), and fluids collected prior to saline abortion (103 samples). Samples contaminated by blood or meconium were excluded. Wherever possible the battery of maturity

tests were done on each sample of amniotic fluid. Tests performed were as follows: the L/S ratio, 463 samples; creatinine, 501 samples; and percentage of lipid-positive cells, 458 samples.

Creatinine was estimated by the Jaffe reaction (Toronto General Hospital modification, with the use of the Technicon Auto-Analyzer method N-11B). Cytology of the amniotic fluid (percentage of lipid-positive cells) was performed according to the method of Brosens and Gordon.[2] The lecithin/sphingomyelin ratio was estimated with a modification of Gluck's original method.[1, 3] We consider that the critical value for the L/S ratio by this method is 3/1.

Assessment of the newborn infant was made by using the chart devised by Battaglia and Lubchenco.[4] Infants below the tenth percentile were considered small for dates (intrauterine growth retardation). The normal graphs were obtained from 285 samples which were taken from 244 patients. In the abnormal group there were 166 patients from whom 222 samples were obtained. There were 105 samples from 36 Rh-sensitized patients. There were 34 pregnant diabetic patients in the series from whom 40 samples were obtained, and these were subdivided according to the White classification. In the Class "A" diabetics there were 16 samples from 12 patients; in Class "B," seven samples from seven patients; Class "C," 16 samples from 14 patients; and Class "D," one sample. The 47 samples from 38 patients with "hypertensive disorders" included 30 samples from pre-eclamptic patients, 13 samples from hypertensive patients, and four samples from patients with superimposed pre-eclampsia. There were 12 pregnancies in which intrauterine growth retardation was diagnosed and from these 24 samples were obtained. Of these 24 samples, seven were obtained from pregnancies which were considered to be otherwise normal, 14 from patients with hypertensive disorders, and three from a Grade III cardiac patient. There were five patients with hydramnios from whom five samples were obtained. One case of hydramnios was associated with an anencephalic fetus, two with normal pregnancies, and one was from a gestational diabetic patient.

Results

Tables I and II show the mean values ±1 standard deviation for the L/S ratio, creatinine, and lipid-positive cells for both the normal and abnormal pregnancies for the various weeks of gestation.

Normal pregnancy. Amniotic fluid creatinine values showed a relatively small standard error throughout gestation, increasing somewhat toward term. The mean values from 15 to 22 weeks were in the region of 0.8 mg. per 100 ml. There was then a slow but gradual rise to 2.1 mg. per 100 ml. at 37 weeks. This was then followed by a less rapid rise and at 44 weeks the mean values were 2.2 mg. per 100 ml. The L/S ratio started in the range of 0.9 at 15 weeks, then rose progressively to a mean value of 3.6 at 34 weeks, 5.7 at 37 weeks, 8.6 at 40 weeks, and 10.4 at 44 weeks. Up to 31 weeks, values were within a fairly narrow range and after 34 weeks there was a much wider spread of values. Percentage of lipid-positive cells showed a very gradual rise to 34 weeks, at which time the average value was 5.9 per cent. Thereafter, the rise was rapid, with a mean of 22.2 per cent at term and a gradual increase to 26 per cent at 44 weeks. There was a fairly narrow range of values from 15 to 34 weeks, with a moderate increase in standard error thereafter.

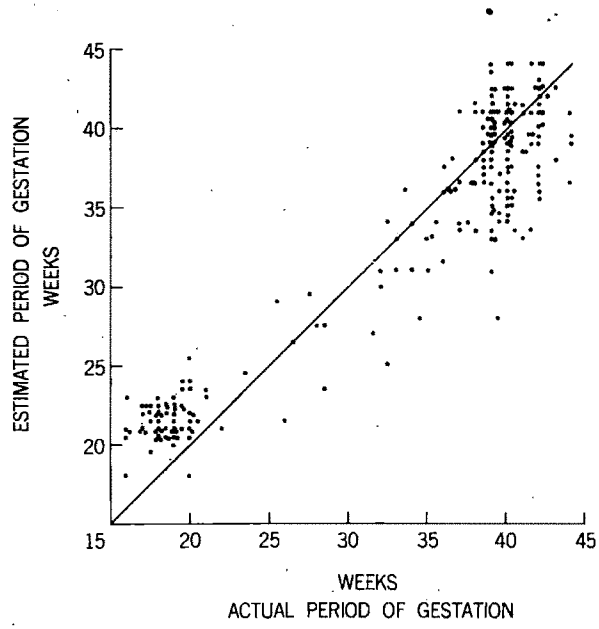


Fig. 1. Estimated vs. actual period of gestation in normal pregnancy (222 samples).

In the normal series there were 285 samples of amniotic fluid from 244 patients. All three parameters were available in 222 samples and the estimated periods of gestation were calculated from these. The coefficient of correlation between the estimated period of gestation based on the three parameters (EPG) and the actual period of gestation (APG) was 0.94 (Fig. 1). When the parameters were analyzed individually, the coefficient of correlation for creatinine was 0.86, for lipid-positive cells 0.92, and for the L/S ratio 0.85.

Abnormal pregnancy states. There were 222 samples of amniotic fluid from 116 patients with abnormal pregnancy states.

Rh isoimmunization. Amniotic fluid creatinine values (Tables I and II) were at the lower range of normal

Table I. Amniotic fluid mean values for normal and abnormal pregnancies ± 1 S.D. (15 to 28 weeks' gestation)

		Weeks of gestation														
		15			*19*			*22*			*25*			*28*		
	Total	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*
Creatinine:																
Normal	285	33	0.8	0.12	64	0.8	0.09	4	0.7	0.08	4	1.0	0.19	5	1.2	0.18
Rh	105	—	—	—	—	—	—	6	0.8	0.11	21	0.9	0.16	25	1.0	0.30
Diabetes	40	—	—	—	—	—	—	—	—	—	—	—	—	1	1.3	0.00
Hypertensive disorders	47	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pre-eclampsia	(30)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IUGR	24	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hydramnios	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
L/S ratio:																
Normal	261	31	0.9	0.25	54	0.8	0.28	4	0.9	0.29	3	1.1	0.28	5	1.5	0.35
Rh	93	—	—	—	—	—	—	6	1.0	0.12	19	1.1	0.30	20	1.5	1.51
Diabetes	40	—	—	—	—	—	—	—	—	—	—	—	—	1	2.1	0.00
Hypertensive disorders	45	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pre-eclampsia	(28)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IUGR	24	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hydramnios	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Lipid-positive cells:																
Normal	261	28	0.1	0.26	59	0.7	2.63	4	0.8	0.83	4	2.2	1.48	5	2.0	1.79
Rh	96	—	—	—	—	—	—	4	2.8	1.48	19	3.7	2.45	23	3.6	4.23
Diabetes	35	—	—	—	—	—	—	—	—	—	—	—	—	1	2.0	0.00
Hypertensive disorders	43	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pre-eclampsia	(30)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IUGR	23	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hydramnios	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

throughout gestation. Mean values and standard deviation of L/S ratios in Rh isoimmunization coincided very closely with those of the normal series. Mean percentage of lipid-positive cells corresponded closely with the normal mean.

There were 22 samples taken from 18 patients with severe Rh disease in which all three parameters were available. This group included: Infants with a cord hemoglobin of less than 10 Gm., where an intrauterine transfusion was done or where the pregnancy resulted in a stillbirth. In this group the creatinine values tended to be lower, yet within the range of the Rh series as a whole, while the values for the lipid-positive cells and L/S ratio were the same as for the entire Rh group.

In 86 Rh samples, where all three parameters were tested, the coefficient of correlation between EPG and actual period of gestation (APG) was 0.77 (Fig. 2). Distribution of values above and below the regression line was 28/57. When the individual parameters were tested, the coefficient of correlation for creatinine was 0.71, L/S ratio 0.59, and lipid-positive cells 0.53. Results in the severe cases seemed identical to the Rh group as a whole, although the number of cases was small.

Diabetes. Creatinine values in diabetes approximated normal mean values (Tables I and II). Mean values of the L/S ratios also followed the normal mean values until week 34, after which they fell below normal mean values but remained within the normal range. Mean percentage of lipid-positive cells in diabetics was below the normal mean values but within the normal range, the difference being greater toward term. The classes of diabetes were reviewed separately with the three key parameters and no distinct trend among the four classes (A, B, C, and D) was noted in any of the parameters.

The estimated period of gestation was calculated as before (Fig. 3) and these were plotted against the actual period of gestation. In the 40 samples from diabetic patients, where all three parameters were estimated the coefficient of correlation between EPG and APG was 0.67. The distribution of results above and below the true regression line was 15/25 and for the individual

Table II. Amniotic fluid mean values for normal and abnormal pregnancies ± 1 S.D. (31 to 44 weeks' gestation)

	Weeks of gestation														
	31			*34*			*37*			*40*			*44*		
	No.	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*	*No.*	*Mean*	*S.D.*
Creatinine:															
Normal	9	1.5	0.25	12	1.6	0.20	25	2.1	0.41	98	2.1	0.50	31	2.2	0.45
Rh	15	1.1	0.30	22	1.4	0.27	15	1.7	0.38	1	1.9	0.00	—	—	—
Diabetes-	4	1.3	0.70	11	1.9	0.54	20	2.1	0.29	4	2.2	0.25	—	—	—
Hypertensive disorders	3	1.6	0.26	12	1.8	0.39	22	2.1	0.63	10	2.1	0.43	—	—	—
Pre-eclampsia	—	—	—	8	1.6	0.22	10	2.2	0.32	10	2.3	0.44	2	2.7	0.10
IUGR	1	1.3	0.00	9	1.5	0.38	11	1.7	0.46	3	2.3	0.24	—	—	—
Hydramnios	—	—	—	1	1.0	0.00	2	1.7	0.82	1	2.2	0.00	1	2.2	0.00
L/S ratio:															
Normal	8	1.5	0.69	11	3.2	3.82	25	5.7	6.22	92	8.6	7.68	28	10.4	7.14
Rh	12	2.0	2.43	21	3.6	3.30	14	5.1	5.32	1	8.8	0.00	—	—	—
Diabetes	4	1.2	0.26	11	4.0	5.64	20	5.2	4.51	4	5.8	4.02	—	—	—
Hypertensive disorders	3	1.6	0.22	10	3.1	2.30	22	4.4	3.04	10	7.3	6.02	—	—	—
Pre-eclampsia	—	—	—	5	2.5	0.72	12	2.7	0.89	8	5.2	2.68	2	12.0	0.10
IUGR	1	1.7	0.00	9	1.6	1.01	11	2.6	1.47	3	4.0	1.41	—	—	—
Hydramnios	—	—	—	1	3.0	0.00	2	3.0	0.18	1	5.0	0.00	1	3.0	0.00
Lipid– positive cells:															
Normal	6	4.5	2.57	9	5.9	3.87	20	14.6	7.83	96	22.2	11.64	30	25.8	10.96
Rh	15	5.5	3.86	21	8.9	7.66	13	11.2	5.35	1	20.0	0.00	—	—	—
Diabetes	4	3.0	0.71	8	3.6	0.99	18	10.0	5.85	4	13.2	6.06	—	—	—
Hypertensive disorders	2	2.0	1.00	10	6.1	3.94	21	13.0	5.34	10	24.0	14.17	—	—	—
Pre-eclampsia	—	—	—	8	6.6	2.39	10	11.3	1.32	10	15.5	2.17	2	10.0	0.00
IUGR	1	3.0	0.00	9	8.3	5.54	11	12.4	5.64	2	35.0	15.0	—	—	—
Hydramnios	—	—	—	1	5.0	0.00	2	10.0	8.00	1	40.0	0.00	1	25.0	0.00

parameters the coefficient of correlation for creatinine was 0.60, lipid-positive cells 0.72, and L/S ratio 0.3.

Hypertensive disorders. Tables I and II show that the mean amniotic fluid creatinine in hypertensive disorders was slightly above the normal mean only at 31 to 34 weeks, whereas L/S ratios were slightly below the normal mean values from 34 weeks to term. Mean percentage of lipid-positive cells coincided closely with the normal range.

In the 30 samples from pre-eclamptic patients, mean creatinine values were above those of the normal series. Mean L/S ratios and lipid-positive cells were moderately lower than the normal values but within the normal range. Creatinine values from 13 hypertensive patients were slightly higher than normal mean values, whereas L/S ratio and percentage of lipid-positive cells were slightly below the normal mean values. This was consistent with the findings of the group as a whole. Three samples from patients with hypertension and superimposed toxemia showed no distinct trend as compared to the normal series but the number of cases was insufficient to draw any conclusion.

The EPG for hypertensive disorders was plotted against the actual period of gestation in 46 samples and the coefficient of correlation was 0.59 (Fig. 4). The distribution of values above and below the true regression line was 24/26. The coefficients of correlation for individual parameters in hypertensive disorders were as follows: for creatinine 0.30, for L/S ratio 0.40, and for percentage of lipid-positive cells 0.67. EPG vs. APG in pre-eclampsia was 0.64.

Intrauterine growth retardation. Mean values for amniotic fluid creatinine were slightly below the normal mean values whereas the values for the L/S ratio were considerably below normal but within the normal mean range. Lipid-positive cells corresponded well with the normal mean values.

The scattergram (Fig. 5) of the EPG vs. the APG in 20 samples demonstrated a distinct lag in estimated period of gestation, with 17/20 values below the true regression line. The coefficient of correlation was 0.61.

Hydramnios. There were five samples of amniotic fluid from five patients with hydramnios. Creatinine and lipid-positive cells were distributed within the

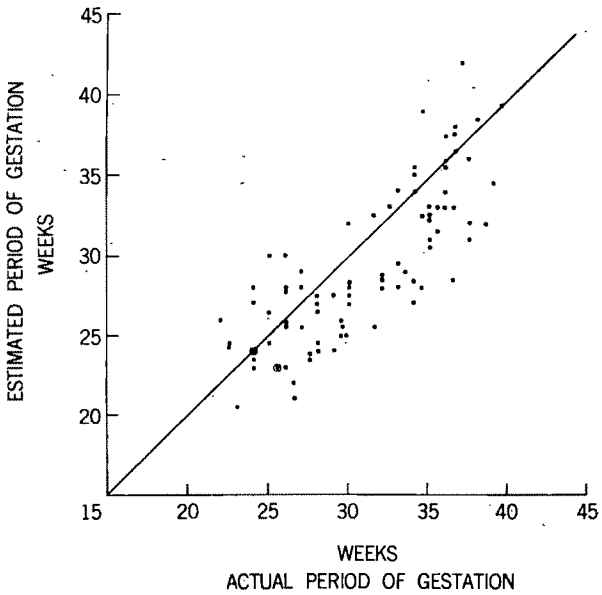


Fig. 2. Estimated vs. actual period of gestation in Rh immunization (86 samples). The circled dots indicate intrauterine hydrops.

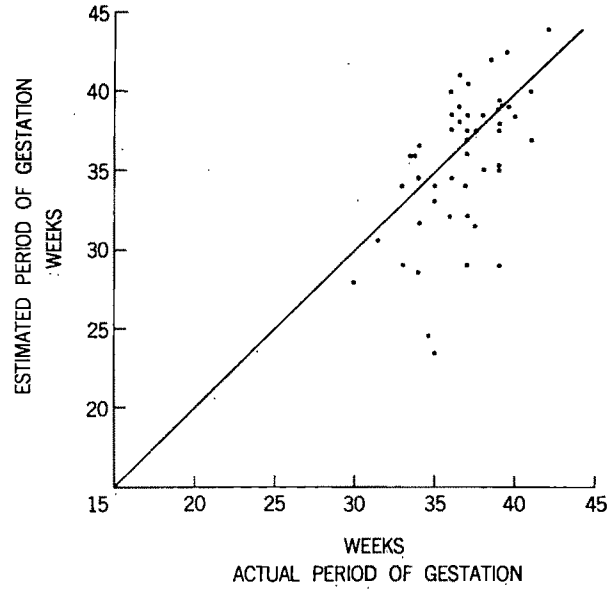


Fig. 4. Estimated vs. actual period of gestation in hypertensive disorders (46 samples).

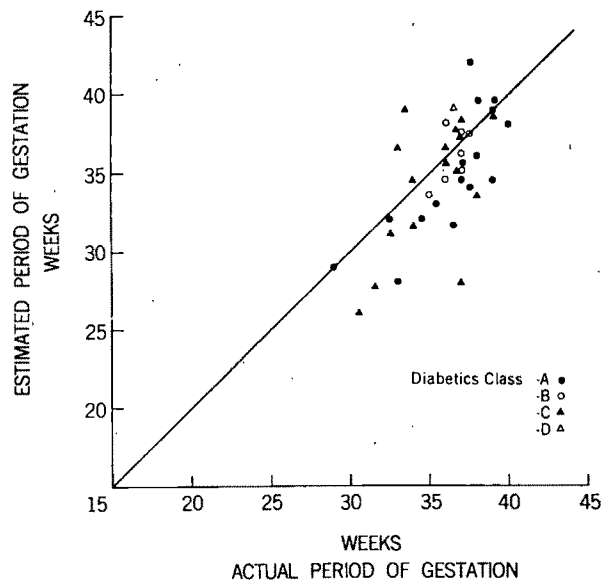


Fig. 3. Estimated vs. actual period of gestation in diabetes (40 samples).

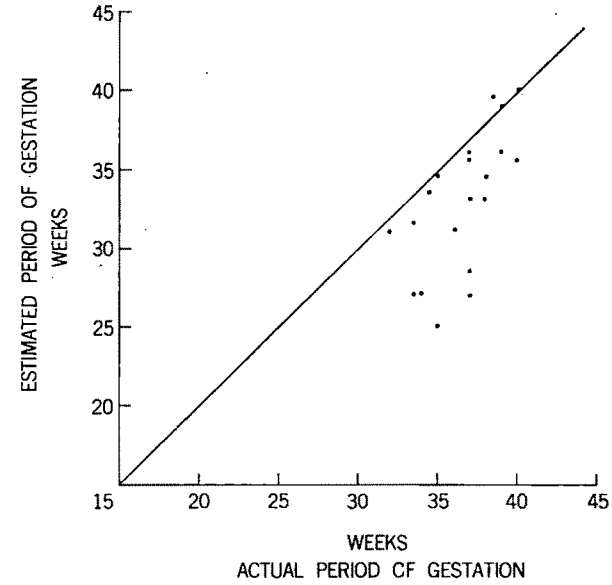


Fig. 5. Estimated vs. actual period of gestation in intrauterine growth retardation (20 samples).

normal range whereas the L/S ratios were lower than the normal mean but within the normal range.

The results of the EPG vs. the APG were insufficient to make any concrete conclusions but the correlation appeared satisfactory with only a slight lag.

Table III shows the relationship of L/S ratio to fetal pulmonary maturity in 150 samples taken from patients within 48 hours of delivery. In the Rh-isoimmunization group, four amniocenteses followed intrauterine transfusion, the interval being 2½ to 4 weeks, and a mature L/S ratio correctly predicted no respiratory distress at delivery in each case.

Comment

When we consider the normal pregnancies in our present series, our findings confirm those of the previous paper in that we had a coefficient of correlation of 0.94 when comparing the EPG (esti-

mated period of gestation) to the APG (actual period of gestation). When the separate parameters were calculated with respect to EPG vs. APG an excellent correlation was obtained but each individual calculation (EPG) was still slightly less accurate than the EPG based on the three key parameters. We can therefore conclude that in normal pregnancy this method of estimating fetal maturity is accurate and that the three-mean method is more accurate than a maturity estimate based on one of the three tests. In this normal series the L/S ratio continued to be accurate in predicting fetal pulmonary maturity but there was a significant number of false-immature tests (14/99 or 14 per cent) in samples taken within 48 hours of delivery.

In our Rh-isoimmunization series creatinine values were moderately lower than normal throughout gestation. This confirms the results of a previous paper[5] and the findings of Hinkley and associates.[6] The coefficient of correlation of EPG vs. APG in Rh disease with lipid-positive cells was not as good as the normal series with a wider scatter but mean values were close to the normal mean. Donnai and associates[7] used a combination of creatinine and lipid-positive cells in assessing maturity in Rh disease and found the combination better than individual results. Our findings were similar in that the combined EPG based on the three parameters correlated reasonably well to fetal maturity, with a coefficient of correlation of 0.77. The distribution of results above and below the perfect regression line (28/57) indicated a slight trend toward underestimating gestational age in Rh disease by this method.

The L/S ratio in our hands was a good indicator of fetal pulmonary maturity in Rh disease with no false positives or negatives in the nine samples taken within 48 hours of delivery. This also held true when amniocentesis followed intrauterine transfusion. In our four cases the interval between intrauterine transfusion and amniocentesis varied from 2½ to 4 weeks. Lemmons and Jaffe[8] found two false-mature L/S values in patients who had had intrauterine transfusion followed by amniocentesis for maturity. There is a possibility that the transfusion-amniocentesis interval was short and that the elevation was a false one due to contamination of the amniotic fluid by blood or other contaminant.

Our findings of identical amniotic fluid creatinine levels in diabetes (primarily Classes A, B, and C) compared to normal pregnancies agree with those of Pitkin and Zwirek[9] and Cassady and associates[10] who also found higher levels in diabetic patients with vascular disease. Morrison and associates[11] found lipid-positive cells useful as a test of fetal maturity in diabetes. Our finding of a depression of lipid-positive cells in diabetic pregnancies has not been described before to our knowledge. Gluck and Kulovich[12] stated that L/S ratios were depressed in Classes A, B, and C diabetes. We also found a depression of the L/S ratio in diabetic patients although only after 37 weeks. Gluck and Kulovich found an acceleration in Classes D, E, and F diabetes but we were unable to confirm this as there was only one Class D diabetic patient in our series. In diabetes the combined EPG was still a moderately good test of fetal maturity, the Class C diabetics showing a wider scatter. The distribution of results above and below the true regression line (15/25) indicated a slight tendency to underestimate fetal maturity in diabetes by this method.

Fourteen samples were taken from diabetic patients within 48 hours of delivery and of the nine mature values, two infants developed respiratory distress syndrome. The paradoxical situation of a lower mean L/S ratio in diabetes combined with a significant number of false-mature L/S ratios suggests that the L/S ratio should be interpreted with caution in diabetes. It may well be that surfactant deficiency is not the only etiologic factor in respiratory distress syndrome in diabetes.

In hypertensive disorders as a whole, creatinine values were slightly higher than normal mean values, L/S ratios were slightly lower, and the percentage of lipid-positive cells corresponded to normal mean values. When the three parameters were combined in predicting fetal maturity the results were only fair, with a coefficient of correlation of 0.59. This was due to a wider scatter of values (Fig. 4) despite an even distribution of results above and below the regression line (24/26). The L/S ratio was reasonably accurate in this group, with no RDS in the 48 hour samples when

Table III. Normal and abnormal pregnancies: L/S ratio and fetal pulmonary maturity samples taken within 48 hours of delivery

	Mature L/S ratio		*Immature L/S ratio*		
	No.	*No. with RDS*	*No.*	*No. with RDS*	*Total no. of patients*
Normal	82	0	17	3	99
Rh	8	0	1	0	9
Diabetes	9	2	5	1	14
Hypertensive disorders	10	0	7	1	17
Intrauterine growth retardation	3	0	5	0	8
Hydramnios	3	0	0	0	3

the L/S ratio was mature but with 6/7 false-immature values. When the pre-eclampsia group was analyzed separately, trends in the entire group of hypertensive disorders were accentuated. Creatinine values were moderately elevated above normal, as was reported by McAllister and associates,[13] whereas lipid-positive cells were depressed in pre-eclampsia in our series. These findings are consistent with those of Dewhurst[14] and Freeman[15] and their colleagues and not with those of Gluck and associates.[16] This failure of acceleration of the L/S ratio in hypertensive disorders together with a significant number of false-immature L/S ratios suggests that if the stress of this process accelerates fetal pulmonary maturity it is not consistently reflected by the L/S ratio.

In intrauterine growth retardation two of the three parameters were lower than the normal mean values, the creatinine being moderately low and the L/S ratio markedly so. We agree with Moore and associates[17] that amniotic fluid creatinine values in intrauterine growth retardation are depressed. Our L/S ratio findings correlated well with those of Dewhurst and associates,[14] who showed that small-for-dates infants had a mean L/S ratio which was significantly lower than the normal mean. Mean lipid-positive cells, however, correlated well with normal values. This finding agrees with those of Sharp[18] who stated that in established dysmaturity the cytologic picture was the same as in the normal pregnancy as skin histology would not be affected by placental insufficiency. The cumulative result (17/20 values below the true regression line) was a distinct trend toward underestimation of true gestational age in intrauterine growth retardation by this method. It is, however, interesting to note that despite five of eight L/S ratios in intrauterine growth retardation being immature within 48 hours of delivery, none of the eight infants developed respiratory distress. Numbers are small but there is a suggestion here of a tendency toward false-immature L/S ratios in intrauterine growth retardation.

The finding in the same patient of depressed biparietal diameters on serial ultrasonography, depressed EPG, and a low urinary estriol output would tend to confirm a diagnosis of intrauterine growth retardation. At the present time we are studying a series of patients by serial ultrasonography and serial amniocentesis in order to assess the relationship between these two parameters.

In hydramnios the combined maturity estimate, EPG, was slightly depressed in the small number of cases studied. This depression was much less than would occur if dilution effect were the only factor. Compensatory mechanisms must therefore operate to maintain levels in the presence of larger volumes of amniotic fluid. Thus amniotic fluid tests for maturity in hydramnios do continue to reflect maturity even in the presence of a marked increase in amniotic fluid volume.

In summary, amniotic fluid tests for fetal maturity in abnormal pregnancy states do, in the main, continue to reflect reasonably accurately true gestational age, particularly if the three key parameters are combined. There are, however, deviations from the normal values in abnormal pregnancy states which should be taken into account by the clinician in assessing fetal maturity in these conditions. Other parameters, particularly the measurement of biparietal diameters by ultrasound should also be utilized in the assessment of maturity in the high-risk fetus.

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Results in treating 210 patients with detrusor overactivity incontinence of urine

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Eighty (72.7 per cent) of 110 patients with detrusor overactivity (in controlled and uncontrolled series) showed improvement with parasympatholytic drug (propantheline bromide or dycyclomine HCl) therapy. Twenty per cent of patients on placebo therapy showed improvement. When standard surgery improved bladder neck funnelling, detrusor overactivity was improved in 77.3 per cent of cases. Surgery failed to improve detrusor overactivity in 54.5 per cent of patients who showed no significant bladder neck funnelling. Bladder neck funnelling appears to be a cause of detrusor overactivity in some women. Results with medical and surgical therapy were not associated with significant change in bladder capacity.

THE TREATMENT of pressure equilization (anatomic or mechanical) stress incontinence of urine in women is quite effective when each case is properly evaluated and the appropriate surgery is performed. The chief limiting factor in achieving complete success in patients so managed is the quality of the local support tissues.[1]

The treatment of detrusor overactivity stress incontinence (detrusor dyssynergia)[4] can be more problematic and the chief limiting factor in more effectively treating these patients, as a group, is our apparent lack of understanding of the mechansims involved in producing involuntary detrusor contraction. There are known causes of detrusor overactivity, but frequently a single cause for detrusor overactivity cannot be clearly identified in a given case and the etiology of the bladder irritability appears to be a complex of known and unknown factors. As a prelude to the purpose of this paper, it would seem appropriate to review the known causes of detrusor overactivity and a new concept developed in this regard in our unit.

Urinary tract infection can be associated with detrusor overactivity; however, elimination of such infection does not always correct detrusor overactivity.

Most, if not all, cases of detrusor overactivity appear to have a neurogenic component. Detrusor overactivity is known to be subject to spontaneous exacerbation and remission. Neurogenic bladders always have some degree of associated detrusor overactivity. A patient on psychotropic drugs often notes an amelioration of her detrusor overactivity when these drugs are stopped. Detrusor overactivity may coexist with a peptic ulcer or spastic colon syndrome. In a recent review, 14 per cent of 50 patients with frontal lobe tumors had symptoms of detrusor overactivity.[5] Patients with detrusor overactivity stress incontinence frequently state that their problem is worse when they hear the sound of running water, have their hands in cold or hot water, or are exposed to cold weather. Parasympatholytic drug therapy may alleviate symptoms related to detrusor overactivity.[3]

Reduced bladder capacity has been associated as a cause and/or effect of detrusor overactivity.

Recently our unit has speculated on funnelling of the bladder neck as a cause of detrusor overactivity in some women. Funnelling of the bladder neck is one of four anatomic changes which are synchronous with or immediately precede detrusor contraction with micturition.[7] Preliminary observation indicated that surgical correction of bladder neck funnelling can correct detrusor overactivity in some women.

The purpose of this paper is to assess the value of parasympatholytic drugs, the value of standard

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surgery for stress incontinence in treating detrusor overactivity stress incontinence, and changes in bladder capacity associated with the forementioned medical and surgical therapy. It was felt that in order to more effectively study the value of each of these forms of therapy, patients with positive urine cultures or with a neurologic bladder or taking psychotropic drugs should be excluded from the study.

Methods and materials

During a 26 month period, 1972 to 1974, 210 patients with detrusor overactivity stress incontinence were treated with drugs or with surgery. The diagnosis of detrusor overactivity stress incontinence was based on both the typical urine loss from a full bladder under stress and intravesical pressure changes characteristic of detrusor overactivity.[3] The patients were divided into three groups.

Group 1. One group of 95 patients was treated medically for detrusor overactivity in an uncontrolled study. Thirteen of these patients had positive urine cultures and were deleted from this report. Of the remaining 82 patients, 18 were treated with dicyclomine HCl (Bentylol, 10 mg. q.i.d.) and 64 were treated with propantheline bromide (Probanthine, 15 mg. q.i.d.) for 3 weeks and then reassessed. The 82 patients in the uncontrolled drug study were tested for evidence of detrusor overactivity stress incontinence (based on clinical loss and bladder pressure studies) after 3 weeks of therapy. The patient was considered cured when she demonstrated neither clinical detrusor stress incontinence nor detrusor irritability on intravesical pressure tracing.[3] The patient was considered improved when there was less clinical loss *and* less detrusor overactivity on the tracing. The result was listed as a failure when the requirements for a cure or an improvement were not met.

Group 2. A second group of 51 patients were entered into a controlled drug study and were placed by random selection on either a placebo, dicyclomine HCl, or propantheline bromide so that each group had 17 subjects. Each patient received a pill (vitamin pill, propantheline bromide 15 mg., or dicyclomine HCl 10 mg.) three times daily for 3 weeks. Two patients were lost to follow-up and six patients had positive urine cultures and were deleted from the study. Of the remaining 43 patients, 15 women received a placebo, 15 received propantheline bromide, and 13 received dicyclomine HCl for 3 weeks and were then reassessed. These 43 patients were assessed in the same manner as the patients in the uncontrolled drug study.

Group 3. Sixty-four patients were treated surgicaly (anterior colporrhaphy or ventral suspension) for their stress incontinence which was entirely due to detrusor overactivity[3] or due to pressure equalization[2] plus detrusor overactivity. Ten patients had a positive urine culture and eight received parasympatholytic drug therapy before or after surgery; these 18 patients were deleted from the study in order to better determine the effects of surgery alone on detrusor overactivity. The remaining 46 patients were assessed 6 weeks following surgery in a manner identical to the drug therapy groups but also had the preoperative and postoperative pressures in the upper centimeter of the urethra compared.

The 46 patients in the surgical series and the 43 patients in the controlled drug series had their pretreatment "full" bladder volume compared with posttreatment "full" bladder volume. In these 89 patients the bladder was filled slowly (approximately 10 c.c. per minute) with normal saline, warmed to body temperature, to the point when the patient felt uncomfortably full.

Observations

Table I shows the result of parasympatholytic drug therapy in the uncontrolled series with 82 patients demonstrating detrusor overactivity stress incontinence. Detrusor overactivity was improved or cured in 74.4 per cent of cases by drug therapy. Of the 18 patients receiving dicyclomine HCl, four were cured, eight were improved, and six were failures (66.7 per cent were at least improved). Of the 64 patients receiving propantheline bromide, 14 were cured, 35 were improved, and 15 were failures (76.5 per cent were at least improved).

Table II shows the results in the controlled series in which a placebo, dicyclomine HCl, or propantheline bromide was used, by random selection, to treat detrusor overactivity stress incontinence. Two patients were cured and one improved (20.0 per cent) with placebo treatment of their detrusor overactivity. The results of using propantheline bromide and dicyclomine HCl were remarkably similar to the results in the uncontrolled series. The mean pretreatment full bladder volume in controlled drug series was 341 c.c., with a range of 200 to 750 c.c. The mean posttreatment volume was 342 c.c., with a range of 150 to 740 c.c. It was decided that significant bladder volume change would be 50 c.c. or more. Only four of the 43 patients showed a significant bladder volume change. One of two patients listed as improved showed a decrease in bladder volume and the other showed an increase in volume after treatment. Similarly, one of two patients listed as failures showed a decrease in bladder volume

after treatment and the other showed an increase in volume.

Table III shows the result of surgery in treating 46 patients with detrusor stress incontinence correlated with pressure change in the upper centimeter or the urethra. Fifty-eight per cent of the 46 patients were at least improved. A significant urethral pressure change was deemed to be 2 mm. Hg. Twenty-two patients showed a "significant" pressure increase in the upper centimeter of the urethra 6 weeks after surgery and 17 (77.3 per cent) were at least improved, whereas only 10 (41.7 per cent) of the 24 patients who showed no change or a significant decrease in their postoperative pressure in the upper centimeter of the urethra were cured or improved. In the series of 46 patients treated by surgery, 35 had pressure equalization plus detrusor overactivity. Of these, 14 (40.0 per cent) were cured, eight (22.9 per cent) were improved, and 13 (37.1 per cent) were listed as failures with respect to effect on detrusor overactivity. All but two of the 35 patients had urethral pressures indicating significant funnelling of the bladder neck (less than 40 mm. Hg pressure in the upper centimeter of the urethra[2]). The other 11 patients had only a detrusor overactivity component to their incontinence and the results were not so good: three (27.3 per cent) were cured, two (18.2 per cent) were improved, and six (54.5 per cent) were failures. The mean preoperative "full" bladder volume was 359 c.c., with a range of 250 to 500 c.c., and the mean postoperative full bladder volume was 391 c.c., with a range of 250 to 500 c.c. in the 46 patients. There was a significant difference in preoperative vs. postoperative bladder volumes in eight cases. Three of these patients were listed as cured: two showed an increase and one a decrease in bladder volume following surgery. One of the eight patients was listed as improved, and she demonstrated an increase in her bladder volume following surgery. Four of the eight patients were listed as failures with respect to the correction of their detrusor overactivity: two showed a decrease and two showed an increase in their bladder volumes following surgery.

Table I. Results of parasympatholytic drug therapy in uncontrolled series of 82 women with detrusor stress incontinence

	Patients		
Result	*No.*	*%*	*Drug used*
Cured	18	22.0	4 dicyclomine HCl 14 propantheline bromide
Improved	43	52.4	8 dicyclomine HCl 35 propantheline bromide
Failure	21	25.6	6 dicyclomine HCl 15 propantheline bromine
	82	100	

Table II. Controlled study using placebo, propantheline bromide, and dicyclomine HCl to treat detrusor stress incontinence

			Result	
Drug	*No. of Pts.*	*Cure*	*Improved*	*Failure*
Propantheline bromide	15	2	+ 9 = 73.3%	4
Dicyclomine HCl	13	7	+ 1 = 61.5%	5
Placebo	15	2	+ 1 = 20.0%	12

Table III. Correlation of surgical result, in treating detrusor stress incontinence, with pressure change in upper centimeter of urethra

	Patients		*Pressure change in upper centimeter of urethra*	
Result	*No.*	*%*	*Increase (no. of patients)*	*Decrease or no change (no. of patients)*
Cure	17	36.9	12	5
Improved	10	21.7	5	5
Failure	19	41.4	5	14
Total	46	100.0	22	24

Comment

The fact that the results of parasympatholytic drug therapy, in the uncontrolled and controlled series, were so similar was reassuring. Although approximately 70 per cent of patients with sterile urine and detrusor overactivity satisfactorily respond to parasympatholytic drug therapy, the clinician is faced with a problem group of patients in which a ready explanation for their detrusor overactivity is not apparent. The fact that some patients respond to propantheline bromide and not to dicyclomine HCl and vice versa suggests different neuromyogenic mechanisms for detrusor overactivity. Those patients who respond selectively to propantheline would seem to have a nerve end plate disturbance and those who respond selectively to dicyclomine HCl may have a fundamental disturbance in the myogenic component of their detrusor muscle contraction. The fact that 20 per cent of patients showed improvement in their detrusor overactivity on placebo must temper one's enthusiasm for the true effectiveness of parasympatholytic drug therapy. Sir John Stallworthy[6] has found ephedrine to be the most effective drug in treating detrusor overactivity, and this observation

suggests receptor site (probably β receptor) response capability in the detrusor muscle. Preliminary work has been reported at this meeting from our unit, indicating that several distinct electromyographic patterns can be demonstrated with coordinate and incoordinate voiding in canine experiments.

In presenting results from surgery in treating detrusor overactivity, the authors would emphasize[1] that, in their opinion, surgery should never be the first approach in treating detrusor overactivity. Hodgkinson and associates[4] have reported an improvement rate of only 26 per cent in 73 patients surgically treated for detrusor overactivity (dyssynergia) stress incontinence. Our improvement rate was 58.6 per cent in 46 patients treated by anterior colporrhaphy or ventral suspension and the better results are probably due to the fact that 35 of the 46 patients had a very definite pressure equalization component to their continence. In this review, improvement was seen in only 45.5 per cent of patients who had pure detrusor overactivity incontinence. Results in Table III, however, indicating 77 per cent improvement in detrusor overactivity when the pressure in the upper centimeter of the urethra was improved, would suggest that correction of funnelling in the bladder neck area improves detrusor overactivity in some patients. At this time, we cannot preoperatively predict which cases of detrusor overactivity will respond when bladder neck funnelling is surgically corrected. It should be noted that funnelling of the bladder neck is usually not associated with detrusor overactivity. It would seem good logic to accept the foregoing concept of bladder neck funnelling as a cause of detrusor overactivity in *some* women when one reflects on the sequence of anatomic change associated with the normal detrusor contraction[7] (micturition). As a result of this review, the current position of our Bladder Physiology Unit is that surgery (designed to correct bladder neck funnelling) should be done only as a last resort to treat detrusor overactivity and only when bladder neck funnelling exists.

The difficulty in standardizing full bladder capacity in different patients was recognized. In comparing significant change in bladder capacities before and after therapy, however, it was felt that the 50 c.c. volumetric latitude helped correct subjective error. Only three of the 89 patients in the controlled drug study and surgically treated group had a pretreatment bladder capacity of less than 250 c.c. Volumetric bladder capacity changes before and after medical or surgical treatment of detrusor overactivity did not appear related to results. The mean bladder capacity in both groups and the entire range of bladder capacities in the surgically treated patients were within normal limits. It is our impression that reduced bladder capacity can be the result of and is probably not a primary cause of detrusor overactivity. When detrusor overactivity exists, an increase in a patient's bladder capacity has the salutory effect of allowing her a longer time interval between episodes of detrusor overactivity but likely does little to correct her detrusor overactivity.

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Cyclic adenosine 3′,5′-monophosphate (cAMP) in pregnancy body fluids during normal and abnormal pregnancy

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cAMP levels in maternal urine (MU), maternal plasma (MP), and amniotic fluid (AF) were measured by competitive protein-binding assay in medically uncomplicated pregnancies (Group A) and some abnormal pregnancies (Group B). In Group A, MU values increased from 3.43 ± 0.3 μMoles per gram of creatinine (mean ± S.E.M.) at 12 to 29 weeks to its peak value, 5.72 ± 1.03 at 33 to 35 weeks ($p < 0.025$). Thereafter, the values decreased until term. In AF, cAMP levels increased from 9.4 ± 1.02 at 10 to 19 weeks to 32.6 ± 2.7 picomoles per milliliter between 35 and 42 weeks ($p < 0.005$). Mean ± S.E.M. MP levels between 4 to 20 and 21 to 42 weeks showed no significant difference (14.97 ± 0.59 and 15.89 ± 0.57 picomoles per milliliter, respectively). Umbilical cord plasma contained higher concentrations than in MP and AF. In Group B, abnormal MU patterns were observed in hypertensive disorders, chronic renal disease, and postmaturity. In a single patient with hyperthyroidism, abnormal MU and AF (but not MP) levels were observed. Abnormalities in MU and AF concentrations of the nucleotide are thus not specific for one disease entity.

RECENT STUDIES demonstrated that the maternal urinary excretion and amniotic fluid concentrations of cAMP increase during normal pregnancy,[1, 2] whereas maternal and umbilical cord plasma cAMP levels have not been well documented. Abnormal amniotic fluid levels and maternal urinary excretion of the nucleotide have been reported in hypertensive disorders associated with pregnancy.[3, 4] The present study was undertaken in an attempt to confirm these findings and extend the observations to include the maternal plasma in subjects with medically uncomplicated pregnancies. Preliminary data from the umbilical cord plasma of three neonates are included in this report. Additionally, two patients with pre-eclampsia and a patient each with chronic renal disease, post-term pregnancy, and hyperthyroidism were studied to determine possible deviations from normal in these disorders during pregnancy.

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Materials and methods

Group A patients. Maternal plasma (MP), maternal urinary (MU), and amniotic fluid (AF) samples were obtained in a cross-sectional manner from medically uncomplicated pregnancies of known gestational ages. Two patients (J. G. and E. T.) were studied longitudinally; umbilical cord plasma was obtained from both infants at delivery. In a third patient (A. H.), MP, umbilical cord plasma, and AF were obtained at the time of repeat elective cesarean section for fetopelvic disproportion.

Collection of samples. MP samples were obtained from an antecubital vein between 09:00 and 15:00 hours. Blood was drawn into tubes containing 0.004 to 0.006M ethylene diamine tetra-acetate (EDTA) as anticoagulant and phosphodiesterase inhibitor.[5] Samples were centrifuged at room temperature within 1

Table I. Clinical data—Group B patients

Pt.	*Age (yr.)*	*Diagnosis*	*Drug treatment*	*Gest. age (wk.)*	*Fetal wt. (Gm.)*	*Placental wt. (Gm.)*	*Other*
S. M.	25 (first preg.)	Pre-eclampsia (edema, hypertension, proteinuria)	Hydrochlorothiazide	38	2,980 (M)	480	ARM and oxytocin; vaginal delivery
B. B.	26 (third preg.)	Chronic renal failure: Congenital absence of left kidney, pyelonephritis of right kidney	40 mEq. Na diet	38	1,890 (F)	350	BP normal, 35-38 wk., C-section; creatinine clearance 38 ml./min./1.72 M.^{2}
M. M.	19 (first preg.)	Pre-eclampsia (edema, hypertension)	None	38	4,160 (M)	530	C-section; no progress in labor
K. L. N.	28 (third preg.)	Hyperthyroidism (partially controlled)	Methimazole, L-thyroxine	38	2,900 (F)	426	C-section; infant euthyroid
A. P.	38 (fourth preg.)	Post-term pregnancy	None	43	3,570 (F)	880	Spontaneous vaginal delivery

hour of collection. Studies in our laboratory and by others[6] revealed that cAMP activity in these samples remained stable up to 20 hours at room temperature. Eighty-eight samples were obtained from 56 patients. Twenty-four hour urine samples were collected with a request that the patient restrict smoking and the intake of caffeine-containing beverages. Forty-eight samples were obtained from 19 patients. AF samples were collected by the methods indicated on Fig. 2. At midpregnancy (10 to 20 weeks), 14 AF samples were obtained by amniocentesis prior to induction of abortion with hypertonic saline for psychiatric indications in medically healthy pregnant women. In late pregnancy (35 to 42 weeks), 13 AF samples were obtained from medically uncomplicated pregnancies. The AF samples were free of meconium or blood contamination and were handled exactly like the MP samples. cAMP activity in these AF samples, as for the MP, was stable for 20 hours at room temperature.

Group B patients. These were patients with pregnancies of known gestational ages complicated by the medical conditions shown in Table I. Thyroid function in K. L. N. was evaluated clinically and biochemically by the Effective Thyroxine Ratio.[7] MU samples from Group B patients and MP and AF samples from K. L. N. were collected as described for Group A patients.

Unless indicated, all patients in the study were free of medication except for routine prenatal iron for at least 6 weeks prior to collection of samples.

All supernatants of plasma, AF, and the filtered aliquots of MU were stored at less than −20° C. and assayed within 1 month.

Assay of cAMP. Plasma and AF samples were prepared for assay after the addition of four volumes of cold ethanol to 0.5 to 1.0 ml. of samples.[8] After mixing, the samples were centrifuged (approximately 2,000 × g) at 4° C. The dried supernatants were then dissolved in 500 μl of assay buffer (Tris-EDTA, 0.05M Tris with 0.004M EDTA—pH 7.5); 50 μl aliquots were assayed for cAMP. Urine samples were assayed directly after diluting 100 μl aliquots, 50- to 100-fold with assay buffer.

The competitive protein-binding assay described by Tovey, Oldham, and Whelan[6] was employed with the cAMP assay kit, TRK 432 (Amersham Searle, U. S. A.). This assay is highly specific for cAMP. Significant interference by ATP, cyclic guanosine monophosphate, phosphodiesterase inhibitors, bivalent metal ions, high salt and high buffer concentrations, as well as fluoride ions, have been excluded.[6] Serial dilutions of plasma and AF produce inhibition curves parallel to those obtained with cAMP standards. In tubes containing cAMP free serum and AF, prepared by incubation with beef heart phosphodiesterase 3′,5′-cyclic nucleotide,* binding of tritiated cAMP was the same as in

*Sigma Lot No. 120C-77519. Two units of the lyophilized enzyme were dissolved in 600 μl of distilled water. Three 100 μl aliquots (total of one unit) were added to 15 ml. of serum (or AF) at 4 hourly intervals. The mixture was incubated at room temperature with continuous stirring for 30 hours.

Table II. Concentration of cAMP in maternal plasma (picomoles per milliliter)

	*Weeks of gestation**	
	4-20	*21-42*
Mean	14.97	15.89
S.E.M.	0.59	0.57
No.	38	50

*Difference between 4 to 20 and 21 to 42 weeks is not significant; $p > 0.1$.

Table III. Concentration of cAMP (picomoles per milliliter) in amniotic fluid

	*Weeks of gestation**	
	10-20	*35-42*
Mean	9.4	32.6
S.E.M.	1.02	2.7
No.	14	13

*Difference between 10 to 20 and 35 to 42 weeks is significant; $p < 0.005$.

control tubes without unlabeled cAMP. Recovery of known amounts of "cold" cAMP added to aliquots of plasma, AF, and urine further confirmed the specificity of the assay.

Repeated assay of pools of plasma, AF, and urine reveal mean between assay CV of less than 12.5 per cent and mean within assay CV of less than 5 per cent. All samples were assayed in duplicate and the standard curve run in triplicate. Assay results were calculated on a programmed desk-top computer (Hewlett-Packard 9810). Data were analyzed by Student's t test.

Urinary creatinine was measured by a modified Jaffe reaction in the Division of Clinical Chemistry, Department of Pathology, University of British Columbia, Vancouver General Hospital.

Results

Group A patients.

MP cAMP concentrations. MP data are shown in Fig. 1 and Table II. Mean ± S.E.M. between 4 to 20 and 21 to 42 weeks were 14.97 ± 0.59 and 15.89 ± 0.57 picomoles, respectively, without a significant difference ($p > 0.1$).

Umbilical cord plasma cAMP concentrations. In subject J. G., neonatal cord plasma cAMP was 61 picomoles per milliliter (Fig. 3), about twofold that of maternal plasma, 31 picomoles per milliliter obtained during labor and the highest MP level in these studies. In ET, cord plasma cAMP concentration was greater than 80 picomoles per milliliter (Fig. 4), several-fold higher

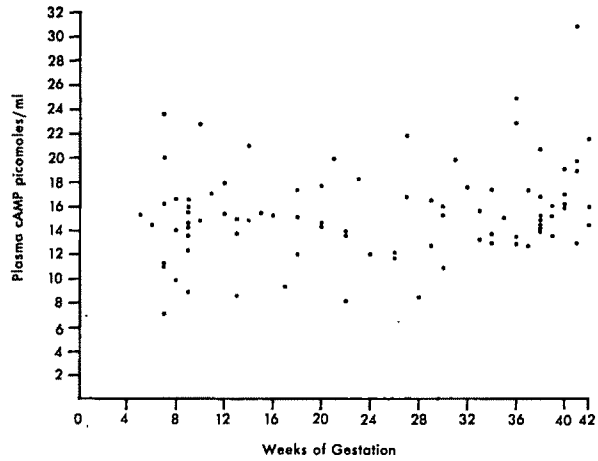


Fig. 1. Plasma concentration of cAMP in normal pregnancy.

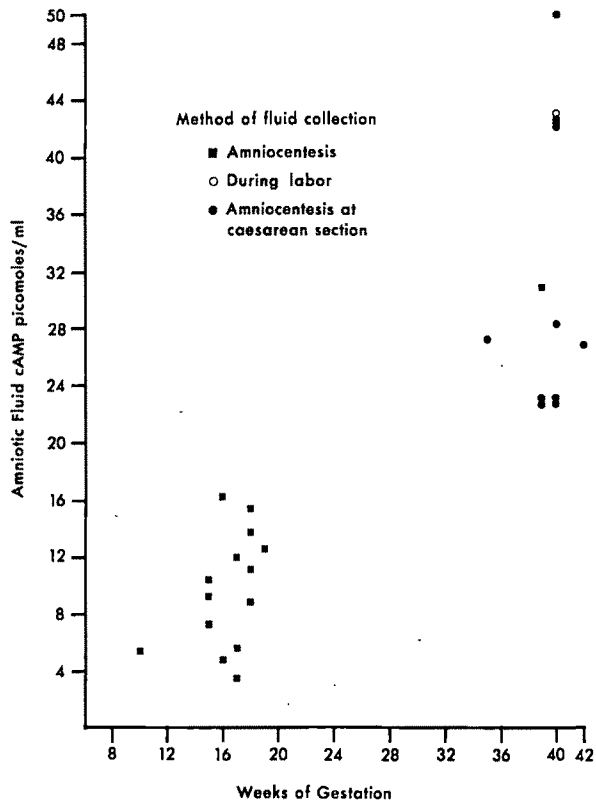


Fig. 2. Amniotic fluid cAMP concentrations in normal pregnancy.

than levels obtained in MP during pregnancy. In AH, simultaneous MP, AF, and cord plasma obtained at the time of repeat elective cesarean section revealed levels of 17, 23, and 46 picomoles per milliliter, respectively.

AF cAMP. AF data are shown in Table III and Fig. 2. Mean ± S.E.M. cAMP levels increased from 9.4 ± 1.02 at 10 to 20 weeks to 32.6 ± 2.7 picomoles per

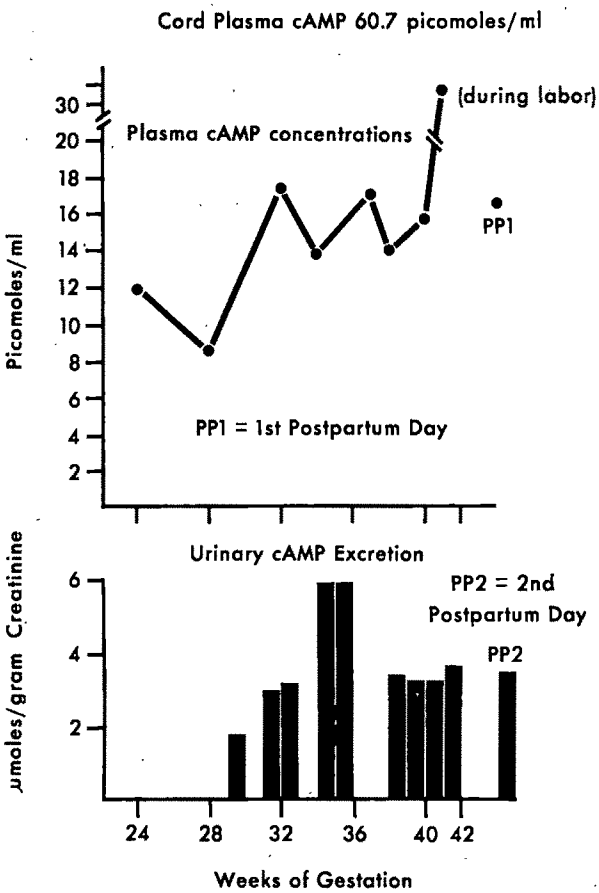


Fig. 3. Patient J. G. serial plasma and urinary cAMP in pregnancy.

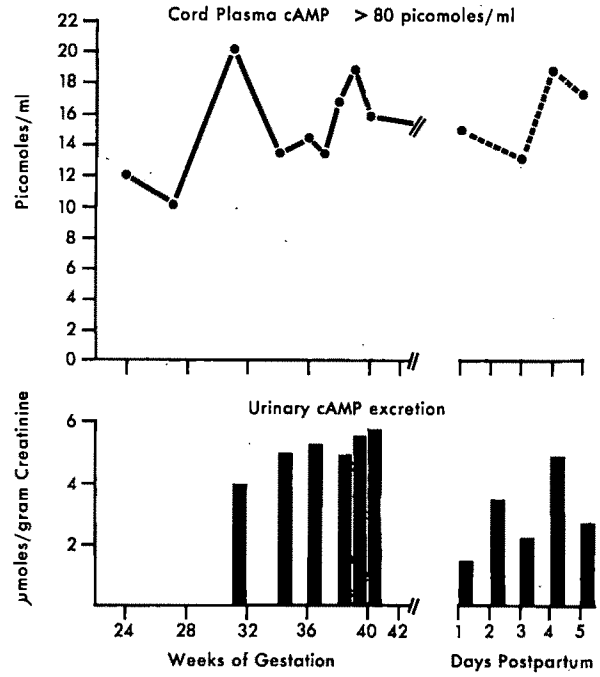


Fig. 4. Patient E. T. serial plasma and urinary cAMP in pregnancy.

milliliter by 35 to 42 weeks. The difference between early and late pregnancy mean values was highly significant ($p < 0.005$).

MU cAMP. Mu data are shown in Table IV and Fig. 5. Mean ± S.E.M. of MU expressed as micromoles per gram of creatinine revealed an increasing trend from 3.43 ± 0.3 at 12 to 29 weeks to a peak of 5.72 ± 1.03 at 33 to 35 weeks ($p < 0.025$); by 36 to 38 weeks and 39 to 42 weeks, the values were 4.94 ± 0.26 and 4.67 ± 0.22, respectively. The findings of the cross-sectional data are supported by the serial studies on J. G. and E. T. (Figs. 3 and 4). There appeared to be a fall in MU (but not MP) values in the first few postpartum days in ET with a wide variation.

Group B patients. As shown in Fig. 6, Patient S. M. (pre-eclamptic toxemia treated with hydrochlorothiazide) had increased MU excretion with a mean value at 37 weeks of 14 μMoles per gram of creatinine. M. M. (pre-eclamptic toxemia not treated with diuretics) had a falling trend in the MU with values essentially in the normal range. In B. B. (chronic renal disease and impaired glomerular filtration) there was a reduction in the MU cAMP from 7.7 to 1.6 μMoles per gram of creatinine at 38 weeks, 1 day before delivery. A. P., with a post-term pregnancy progressing beyond 43 weeks, had increasing MU cAMP excretion to 16.5 μMoles per gram of creatinine 1 day before delivery. Amniocentesis at 41 weeks revealed a normal AF cAMP level of 35 picomoles per milliliter. In K. L. N. (Fig. 7), a pregnant hyperthyroid patient poorly controlled with methimazole in the third trimester of pregnancy, urinary excretion of cAMP was also above the normal range. As the dose of antithyroid drug was increased, clinical improvement was associated with a falling urinary cAMP excretion. The MP cAMP concentration was within the normal range and the AF cAMP was 67 picomoles per milliliter, above the normal range. The fetus was euthyroid at the time of elective cesarean section.

The Apgar scores of the infants in both groups were 7 or above at 5 minutes.

Comment

Our data for midpregnancy (10 to 20 weeks) revealed mean AF concentrations of 9.4 picomoles per milliliter and in late pregnancy (35 to 42 weeks), 32.6 picomoles per milliliter. We thus confirm the increasing trend of cAMP between mid and late pregnancy amniotic fluids reported by Ling and associates.[2] However, our mean values were approximately

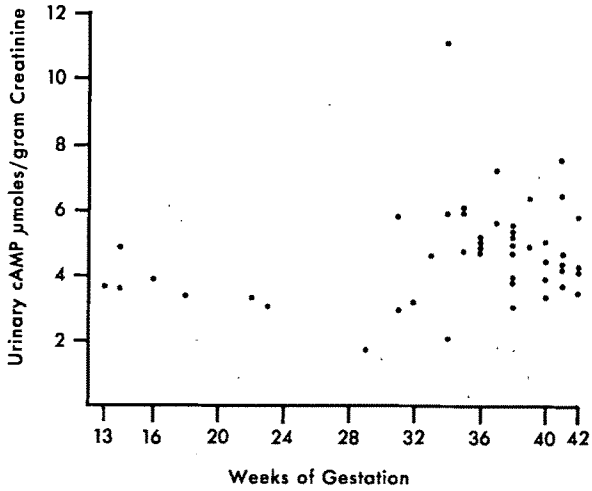


Fig. 5. Urinary excretion of cAMP in normal pregnancy.

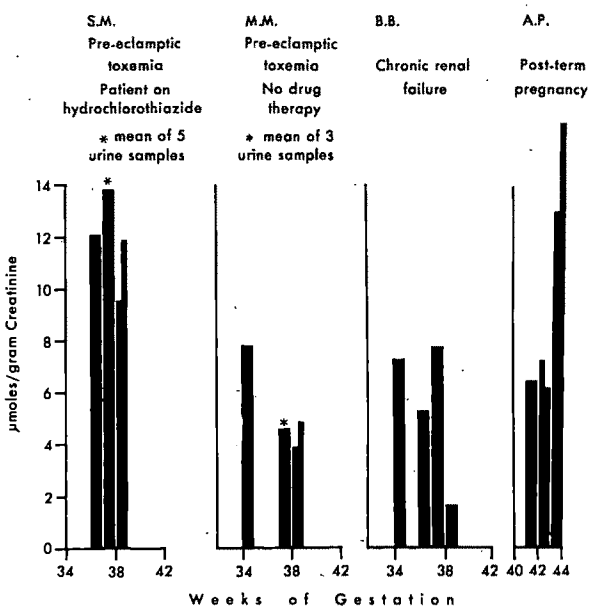


Fig. 6. Urinary excretion of cAMP in hypertensive disorders of pregnancy, chronic renal disease, and post-term pregnancy.

twofold higher. The specificity of the assay we employed[6] suggests that cross-reactivity with other nucleotides in biologic fluids was unlikely to account for the higher values we observed. In midpregnancy (10 to 20 weeks), the mean concentration of cAMP in the AF was approximately 50 per cent that of maternal plasma. By contrast, in late pregnancy (35 to 42 weeks) the mean AF concentration was in excess of twofold that of the MP.

Increased urinary excretion of cAMP from early to late pregnancy was initially reported by Taylor and associates,[1] who found elevations from the twelfth week

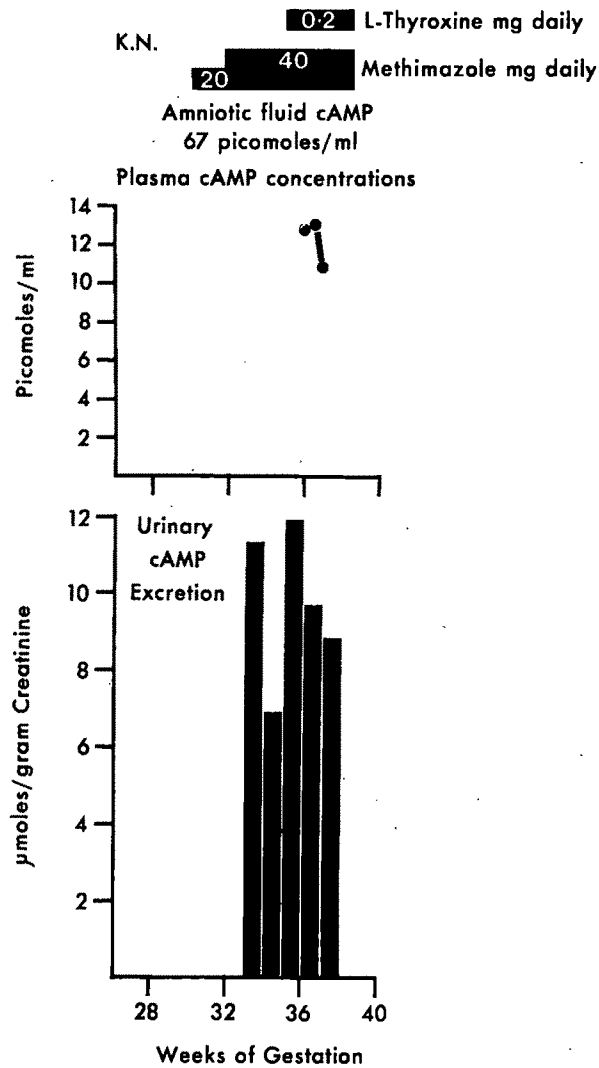


Fig. 7. Hyperthyroidism in pregnancy.

to term. This has also been observed by Raij and associates.[4] As shown in Table IV, the mean cAMP excretion increases by 60 per cent from 3.43 (before 30 weeks) to 5.72 μMoles per gram creatinine at 33 to 35 weeks, where the highest levels are reached.

In contrast to the AF and MU, the mean plasma concentrations showed little variation throughout pregnancy. The levels we observed were comparable to that of the nonpregnant state.[9] The homeostatic mechanisms controlling the plasma level of the cyclic nucleotide thus appeared to maintain a steady concentration throughout pregnancy. Our samples were obtained from 09:00 to 15:00 hours during the day and the variation observed in our data may possibly be due to diurnal or other effects on cAMP levels in maternal plasma. Three cord blood samples contained cAMP levels several-fold higher than in maternal

Table IV. Excretion of cAMP in maternal urine (micromoles per gram of creatinine)

	Weeks of gestation				
	*12-29**	*30-32*	*33-35**	*36-38*	*39-42*
Mean	3.43	4.21	5.72	4.94	4.67
S.E.M.	0.3	0.89	1.03	0.26	0.22
No.	8	3	7	14	16

*Difference between 12 to 29 and 33 to 35 week means is significant; $p < 0.025$.

blood. In patient A. H., simultaneous MP, AF, and cord blood cAMP measured at the time of repeat elective cesarean section revealed higher concentrations in cord blood as compared to the AF and MP.

A patient with pre-eclampsia on hydrochlorothiazide (S. M.) had markedly elevated urinary cAMP excretion. M. M. (pre-eclampsia but not on medication) had a falling trend within the normal range preceding induction of labor. Similar findings (data expressed as micro Moles per 24 hours) have previously been reported.[4] B. B. (impaired renal function) had a low value 1 day preceding delivery by elective cesarean section when the urinary cAMP level fell to 1.6 μMoles per gram of creatinine, the lowest value obtained in the study. K. L. N. (hyperthyroidism) had high urinary cAMP values while clinically and biochemically out of control on medical therapy. As the dose of antithyroid drug was doubled and control of the disease achieved, the cAMP values in urine started to fall concomitant with the improvement noted clinically. The MP values were normal while the AF concentrations were markedly elevated. The infant was clinically euthyroid at delivery by elective cesarean section. A. P., with post-term pregnancy, had high MU cAMP excretion as pregnancy progressed into the forty-third week.

Abnormalities in urinary excretion of cAMP during pregnancy are thus nonspecific and may be the result of diuretic therapy. Abnormally high AF and MU values may be found in hyperthyroidism in association with normal MP levels. Thus, increased AF levels are also nonspecific, since this has also been reported in pre-eclamptic toxemia and chronic hypertension.[3] Further evaluations of cAMP levels in pregnancy body fluids are required to determine the clinical significance of these findings.

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Electromyographic and pressure studies in the canine bladder

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The dog is unable to void until funnelling of the bladder neck occurs, even when the bladder is stressed with a large volume and with parasympathomimetic drugs. Nil or very little pressure rise occurs just prior to micturition. Well-coordinated voiding is associated with simultaneous electrical activity in either the upper urethra and bladder neck or these two areas plus the fundus, with predominance of electrical activity (frequency and amplitude) in the bladder neck in both circumstances. Incoordinate electrical activity is seen in the bladder fundus, bladder neck, and upper urethra with incoordinate voiding.

PERPLEXED BY the problem of detrusor overactivity refractory to standard therapy and the problem of bladder dysfunction following surgery for stress incontinence,[1–3] our unit has become interested in studying patterns of detrusor contractility in the canine bladder in the hope that useful information might be obtained which could be extrapolated to the human female bladder and perhaps serve as a preliminary model for future investigative studies on the human bladder. There is a fair amount of information on the innervation and pharmacology of the detrusor muscle in man and in experimental animals.

Micturition basically involves a sacral sensory motor reflex, with central inhibitory control from the cerebrum and midbrain and facultatory control from the anterior pons and posterior hypothalamus.[9] The fundus of the bladder receives sensory innervation from the hypogastric nerve.[9] The bladder neck and trigone receive sensory innervation from the pelvic nerve, and the sensory innervation to the urethra is via the pudendal nerve.[9] The motor nerve to the bladder is the pelvic nerve, providing sacral parasympathetic outflow to the detrusor muscle.[9] Parasympatholytic drugs are effective in correcting detrusor overactivity in approximately 70 per cent of patients with detrusor overactivity stress incontinence.[3, 8] Whether or not sympathetic fibers have motor function is controversial. Sir John Stallworthy[12] has indicated success in treating detrusor

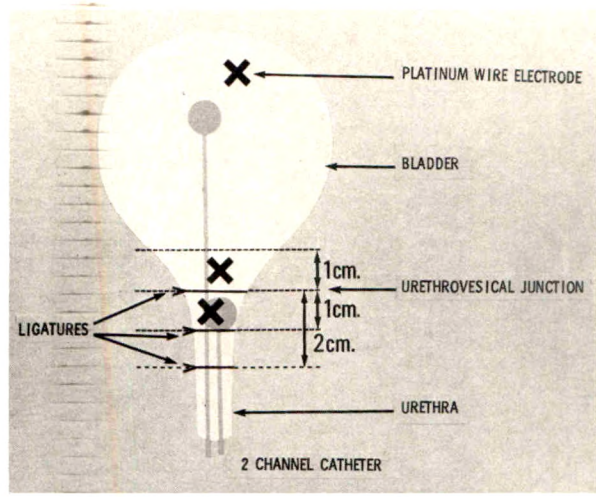


Fig. 1. Diagram shows location of pressure tips (balloon), electrodes, and sutures in canine bladder and urethra.

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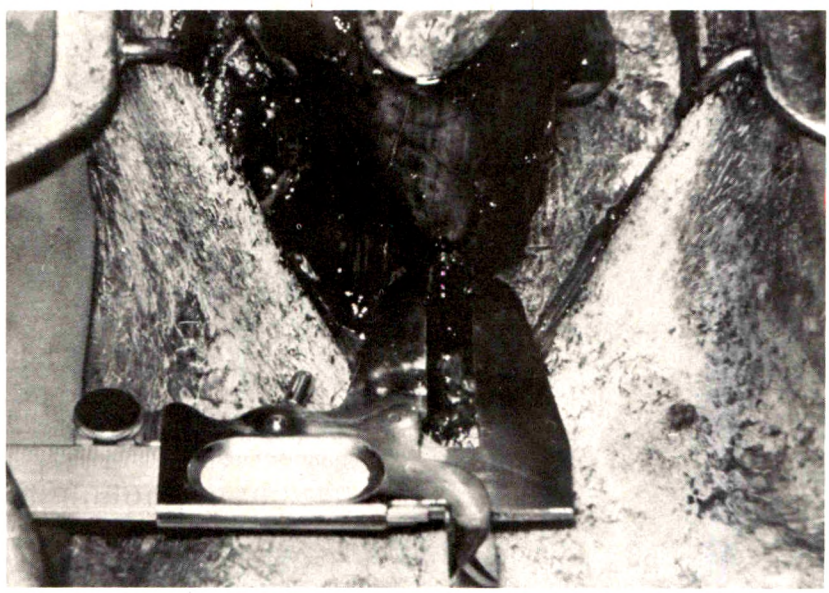


Fig. 2. Bladder, bladder neck, and upper urethra of dog exposed with bladder neck and upper urethral "noncompressing" circumferential sutures in place.

overactivity in the human female with ephedrine. Woodbarne[13] says sympathetic nerves transmit the sensation of pain from the bladder but have no motor function in the human subject. Elmer[5] has reported that adrenaline relaxes the musculature of the rat bladder. Elmer[5] and Siggs[10] have reported that noradrenaline usually relaxes the detrusor muscle in the rat and cat, respectively. Alpha (inhibitory) and beta (excitatory) receptor sites have been demonstrated in the detrusor muscle of experimental animals,[11] but their existence in the human bladder has not been finally established. Bradley[4] has described an "on-off" relationship between the hypogastric nerve (sensory) and the pelvic nerve (motor) in the cat bladder. He has demonstrated that there is a burst of electrical activity in the hypogastric nerve just prior to voiding and immediately after voiding, with no interval electrical activity during voiding, whereas the reverse is true in the pelvic nerve and adjudged by neurogram studies.[4]

Very little work has been reported in studying patterns of detrusor contraction,[6, 7] and the purpose of this presentation was to study the gross anatomy, pressures, and electrical activity in the canine urethra, bladder neck, and fundus of the bladder during vesical filling and micturition.

Methods and materials

Twenty-two healthy, nonpregnant female dogs weighing 13 to 17 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram of body weight). In each instance, an endotracheal tube and femoral vein catheter were introduced. The abdomen was opened through a midline incision extending from the symphysis pubis approximately 15 cm. cephalad. A platinum (or silver) wire electrode was inserted into the detrusor muscle just under the serosal surface in the fundus of the bladder (anterior aspect), in the anterior aspect of the bladder neck area (within 1 cm. of the apparent urethral vesical junction), and in the anterior aspect of the urethral musculature (within 1 cm. of the urethral vesical junction). The electrode preamplifiers were calibrated so that a deflection of 10 mm. on the recording paper was equivalent to 0.5 mv. A two-channel polyethylene catheter with an outside diameter of 4 mm. was then placed transurethrally so that the open-ended tip of one channel was located in the lumen of the bladder and the other open-ended tip was located in the upper centimeter of the urethra. The electromonometer was calibrated so that a deflection on the recording paper of 10 mm. was equivalent to 10 mm. Hg pressure change. The paper speed was set at 10 mm. per 4 seconds. Initially, the dog's bladder was filled at a variable but known rate through a No. 18 gauge catheter with the ureters ligated close to their bladder termination. Later in the series, the dog's bladder was filled with its own urine, using the technique of a rapid intravenous infusion of Ringer's lactate or normal saline. In four dogs, silk sutures were tied snugly around the urethra but in a manner which did not constrict the urethra. These sutures were placed at the urethrovesical junction, and at 1 and 2

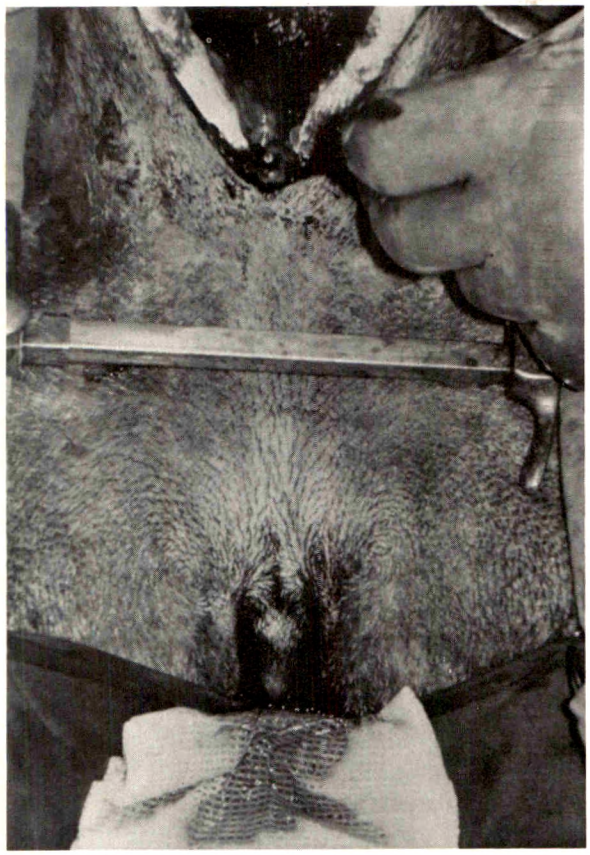


Fig. 3. Bladder neck suture has been cut. Bladder neck funnelling has occurred. Upper urethral suture remains uncut and has descended from view. Dog voids.

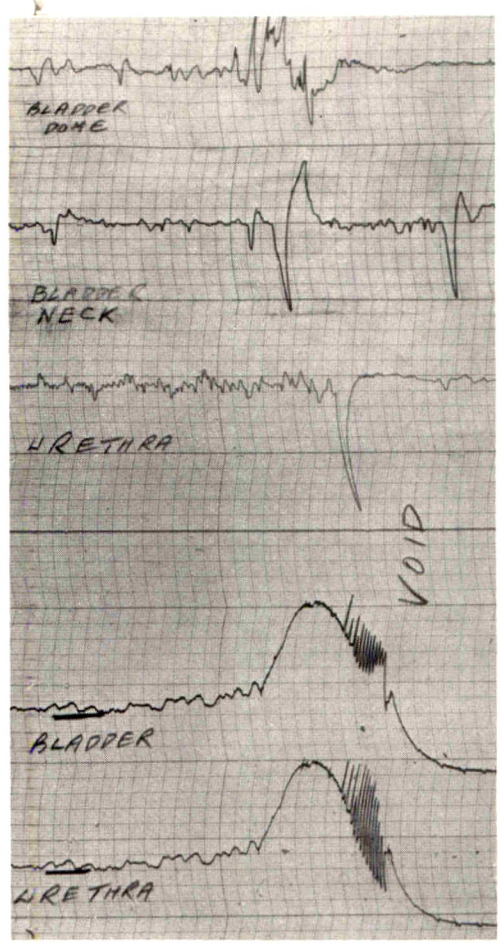


Fig. 4. Simultaneous electromyographic tracings in bladder fundus and neck, and upper urethra, and pressure tracings from bladder and upper urethra (top to bottom). Note graduate rise from baseline bladder pressure to triggering pressure just prior to voiding. (See text for details.)

cm. distal to that junction. Following placement of these sutures, a No. 12 rubber catheter could be passed into the bladder with ease. Fig. 1 shows the placement of the electrodes, sutures, and pressure-recording catheter in the experimental model.

The first 10 dogs in the study were put to death in the development of an experimental model, including the four dogs in which the effect of placing circumferential sutures around the urethra at various levels was studied.

Observations

It was noted that the four dogs with the urethral sutures were unable to void until the suture at the urethrovesical junction or the suture at the urethrovesical junction plus the suture 1 cm. distal to that junction were cut, allowing for a funnelling anatomic change in that area (see Figs. 2 and 3). In two of these dogs, voiding did not occur until the urethrovesical junction suture was cut, even though the bladder was tremendously overdistended with fluid and the detrusor muscle was being stimulated with 0.5 mg. doses of carbamylcholine chloride given through a catheter in the superior vesical artery.

In all experimental models, very little pressure change occurred in the bladder and urethra as the bladder filled until just prior to micturition. A rapid triggering bladder pressure rise of 10 to 30 mm. Hg developed within 2 seconds of the onset of micturition so that voiding could be imminently predicted in every case (see Fig. 4). The final spike of triggering bladder pressure developed after a slow (2 to 10 seconds) or rapid (less than 2 seconds) rise (associated with slow or rapid filling of the bladder, respectively) in baseline bladder pressure to 2 to 4 mm. Hg. Following a well-coordinated void, the bladder pressure returned to the baseline (zero set at 3 to 5 mm. Hg). When the dog voided in an incoordinate and ineffectual

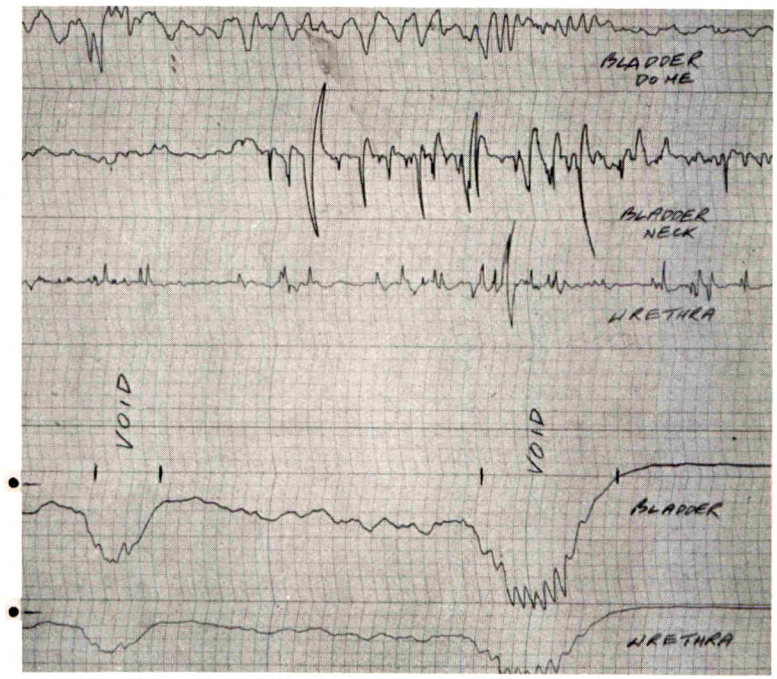


Fig. 5. Tracing in same order as Fig. 4 but reversal (inversion) of pressure tracings, showing initially ineffectual void with electrical activity mostly limited to fundus, followed by synchronous electrical activity in all three areas, with typical predominance of bladder neck activity and good void with bladder pressure returning to below baseline. Asterisks indicate baseline pressure.

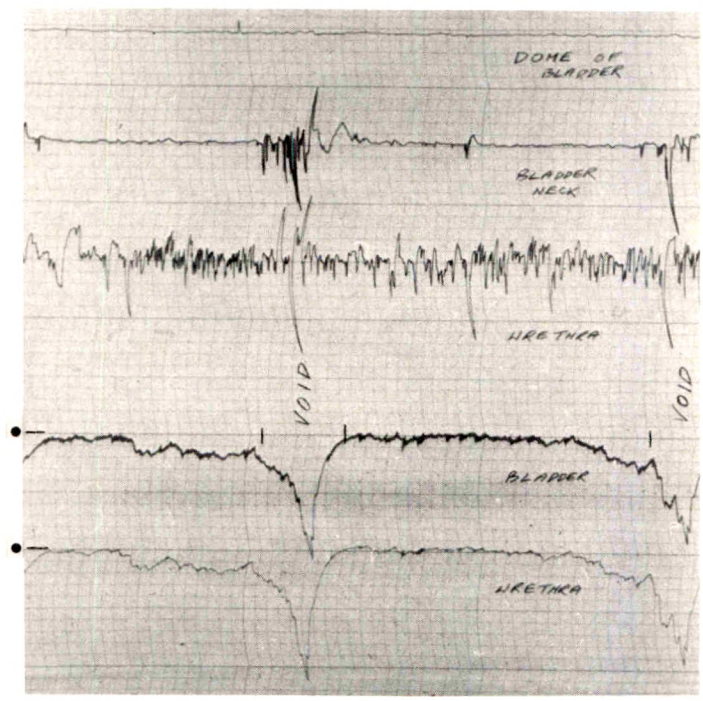


Fig. 6. Tracings in same order and same pressure recording as Fig. 5, showing synchronous electrical activity in bladder neck and upper urethra, with nil activity apparent in fundus, associated with well coordinated void with postvoid bladder pressure back to basline. Asterisks indicate baseline pressure.

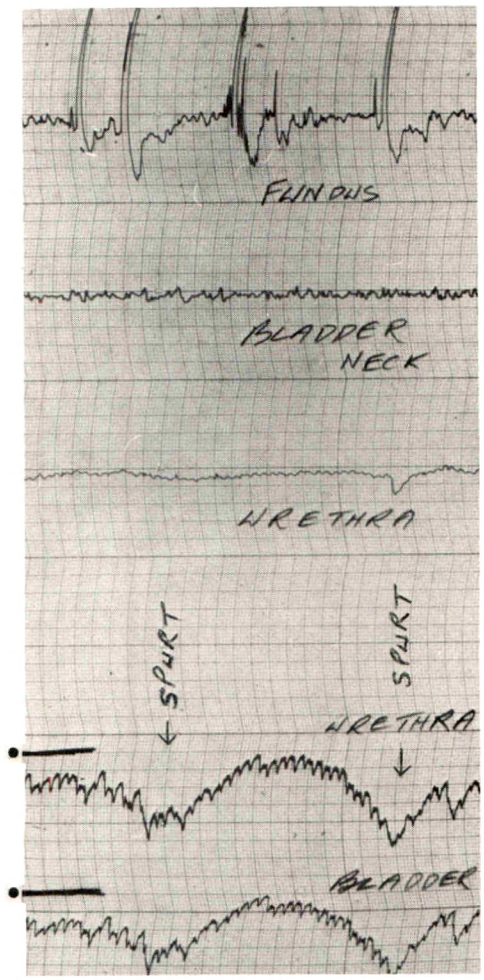


Fig. 7. Tracing in same order and same pressure recording as Figs. 5 and 6, except order of urethral and bladder pressures reversed, showing terminal squirt voiding after normal void with electrical activity only in fundus of bladder. Asterisks indicate baseline pressure.

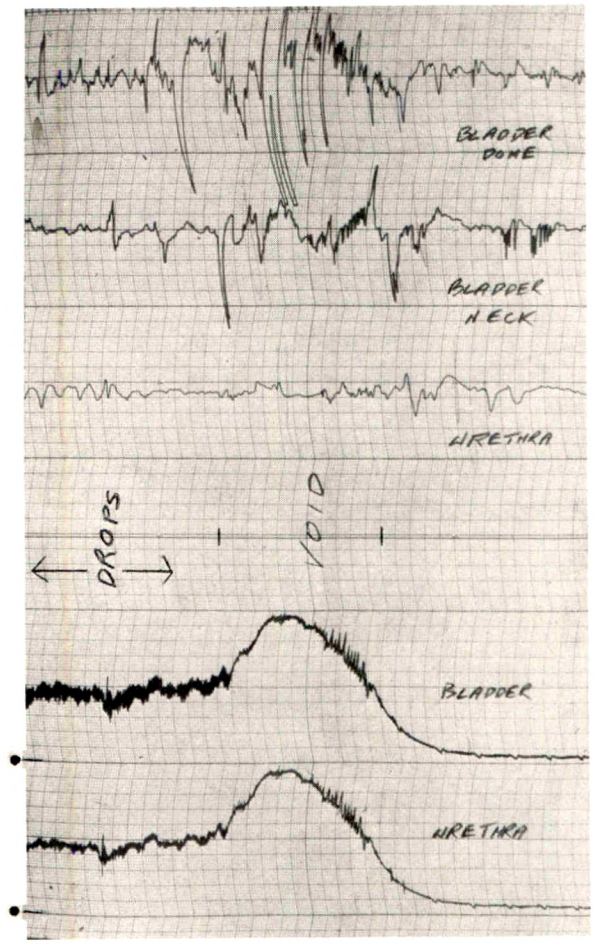


Fig. 8. Tracing in same order and same pressure recording as Fig. 4, with incoordinate electrical activity in all three areas with only drops of urine passed, prior to fairly well coordinated void at time of major pressure rise. Note sustained pressure rise while only drops of urine passed. Asterisks indicate baseline pressure.

manner—in dribbles or low-pressure spurts—the intravesical pressure did not return to the baseline until more effective voiding occurred.

Four distinct electrical patterns were noted during canine micturition. Two of these electrical patterns appeared to be associated with well-coordinated voiding, the latter reflected by a sustained urine stream of good pressure. One of these patterns showed synchronous fundal, bladder neck, and urethral electrical activity (Fig. 5). The other pattern showed bladder neck and urethral electrical activity with no apparent fundal electrical activity (Fig. 6). This latter pattern was most interesting, as it was obvious that the fundus of the bladder was contracting at the time of micturition and yet there was no detectable electrical activity in that area. A third electrical pattern seen in the canine bladder showed asynchronous fundal, bladder neck, and urethral electrical activity associated with incoordinate voiding in the form of drops or short dribbles of urine frequently associated with straining and/or shivering by the dog (Fig. 7). The fourth electrical pattern associated with micturition showed only fundal electrical activity with no apparent electrical activity in the bladder neck or urethra (Fig. 8). This pattern was seen in only four dogs and followed what appeared to be a normal well-coordinated void (with one of the first two electrical patterns described and a "normal" stream of urine, etc.) and was associated with a small "terminal" spurt of urine and noticeable straining by the dog to complete the emptying of its bladder.

Comment

Funnelling of the human bladder neck has been described as an anatomic change seen with micturition by the human female.[13, 14] From our study, it appears to be a mandatory change for micturition in the anesthetized female dog. Perhaps "funnelling" is an absolutely necessary anatomic change when the human female voids, and inability "to funnel" following bladder neck surgery for stress incontinence may be an important reason for the delay in satisfactory voiding following such surgery.[2]

The finding of a triggering pressure rise prior to voiding confirms the same observation by Fredricksen[6] in the anesthetized dog. Whether or not such a pressure rise occurs prior to voiding in the unanesthetized dog is not known, but previous work in the unanesthetized human female has indicated that no intravesical pressure rise occurs with physiologic filling of the bladder until the woman voids.[1] Our work also confirmed Fredricksen's observation that there is very little or no pressure rise in the canine bladder as it fills and perhaps no pressure rise would occur if the dog were not anesthetized and able to cortically suppress the increasing urge to void.

The electromyographic studies suggest that an orderly contractile pattern is required for normal voiding. Jepson and Martin[7] concluded from their canine detrusor electromyographic studies that "all areas of the detrusor and its continuation into the upper urethra contract synergistically in unison." The present work also demonstrated that the bladder neck area is electromyographically prominent in a well-coordinated void. In the second type of electromyographic pattern associated with good voiding, no electrical activity was detected in the fundus. It may have been there and have gone undetected or the detrusor muscle may have not only neuromuscular but also myogenic contractile capability. The third pattern demonstrating an incoordinate type of electromyographic activity and also associated with incoordinate voiding was most interesting and perhaps a similar lack of coordination may be another explanation for delayed voiding and incomplete emptying of the bladder following pelvic surgery.

We plan to extend this work to study, in similar fashion, bladder function in the unanesthetized dog and bladder function in the human female at the time of pelvic surgery.

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Maternal, fetal, and intra-amniotic hormonal and biologic changes resulting from a single dose of hydrocortisone injected in the intra-amniotic compartment

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A single intra-amniotic injection of 500 mg. of hydrocortisone sodium succinate was done 48 hours before elective cesarean section in nine patients in week 39 of gestation. Following that single injection, estriol values fell in all three compartments. Cortisol was rapidly increased in the maternal compartment but returned to normal levels at the time of cesarean section in maternal and umbilical vein cord plasma while remaining elevated in the amniotic compartment. Progesterone was increased in the fetal and amniotic compartments but remained essentially unchanged in the maternal compartment. The foam test was constantly improved in the direction of an intermediary or positive test and the quantitative lecithin-sphingomyelin values were increased by almost twofold. In our series, none of our babies developed a respiratory distress syndrome nor had any difficulty with the first breath or the Apgar score. We did not deliver any low-birth-weight infants and the creatinine values were even improved by our injection.

IT WAS SUGGESTED[1, 2] that an insufficient amount of surfactant, pulmonary immaturity, and respiratory distress syndrome could be linked together. A certain selectiveness of drugs and substances on fetal tissues,[3] and especially lungs,[4–6] has also been suggested. In animals, corticosteroids will enhance pulmonary maturation and improve the survival rate of premature offspring.[7] In human subjects, the findings of Murphy[8] have provided a physiologic justification for the prepartum treatment of respiratory distress syndrome with glucocorticoids.

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In human beings corticosteroids given *intramuscularly*[9] have produced worthy results. However, due to the excellent results obtained in animals by using the intra-amniotic route,[7] we have decided to explore this latter approach. We have tried to detect some of the hormonal and biologic changes in the fetus, mother, and placenta resulting from a single intra-amniotic injection of hydrocortisone sodium succinate. Estriol, cortisol, progesterone, qualitative and quantitative lecithin, and creatinine are the major hormonal and biologic changes that we report in this article.

Material and methods

We report here the results obtained from nine patients scheduled for elective cesarean section, in week 39 of gestation, due to cephalopelvic disproportion, repeat cesarean section, or prior uterine and vaginal surgery. Their ages ranged from 18 to 30 years (mean, 25). Four were primigravidas, four were

Table I. Quantitative analysis of lecithin and sphingomyelin in amniotic fluid

No. of specimen	*Tests of Clement*	*Quantitative dosage L + S*		
		Mean value	*μM ± S.D.*	*Variation*
34	Negative	59	±26	21-119
21	Intermediate	119	±23	77-152
30	Positive	235	±75	137-445

secundigravidas, and one had four pregnancies. The fetal age was also verified by ultrasonography, scanning, and radiologic fetal bone age; all were reported to be of at least 37 weeks' gestation.

Following fetal ultrasound, scanning, and radiologic fetal bone age reports, amniocentesis was performed and 500 mg. of hydrocortisone sodium succinate (Solu-Cortef) were injected into the intra-amniotic fluid. Exactly 48 hours later a second amniocentesis was performed, followed shortly by the proposed cesarean section.

Maternal plasma estriol, cortisol, and progesterone were determined daily, before and after amniocentesis and cesarean. In the amniotic fluid we measured estriol, cortisol, progesterone, foam test (qualitative lecithin-sphingomyelin), quantitative lecithin-sphingomyelin, and creatinine. From the umbilical cord vein plasma we determined plasma estriol, cortisol, and progesterone.

The cortisol and progesterone contents were determined individually, in duplicate, with protein displacement methods.[10, 11] The estriol content was determined in duplicate with a radioimmunoassay.[12]

The total surfactant in amniotic fluid was measured by the rapid test of Clements and associates.[13] The lecithin-sphingomyelin content of the amniotic fluid was measured as follows: amniotic fluid extraction according to Gluck and associates;[14] evaporation of organic solvent; chromatography of residue on 1 cm. of neutral aluminum (AG-7 Bio-Rad);[15] complete elution of lecithin and sphingomyelin with chloroform: methanol 1 : 1; the phospholipid content is determined according to Wuthier.[16] Our results for normal control cases are reported in Table I.

Results and comment

In the amniotic fluid, estriol determinations were constantly lower 48 hours after injection (Table II). The mean value of estriol was reduced by almost half (82.3 to 47.4). At the same time, cortisol values were increased eightfold (5.5 to 41.9) and progesterone 2½ fold (22.6 to 61.9).

In the amniotic fluid (Table III) we were also able to observe a constant improvement in the foam test, the quantitative lecithin-sphingomyelin, and creatinine measurements. All negative foam tests became intermediary 48 hours after hydrocortisone sodium succinate injection and all intermediary results became positive. Except in one case, the quantitative measurements of lecithin-sphingomyelin were increased almost twofold.

In maternal plasma (Table IV), a 2½- to 10-fold reduction in estriol values was constantly observed after hydrocortisone injection in the intra-amniotic compartment. This fall was still found 48 hours after injection. Cortisol values increased threefold within 24 hours after injection and returned to preinjection levels within 48 hours. Progesterone levels were not constantly modified one way or the other by hydrocortisone intra-amniotic injection.

Blood was drawn from the umbilical cord vein at the time of fetal delivery by cesarean section (48 hours after hydrocortisone intra-amniotic injection). Estriol, cortisol, and progesterone were measured in six cases and compared to values given for normal cases with no prior injection (Table V). Estriol values were decreased by at least twofold, progesterone values were increased by 1½- to 10-fold, and cortisol values remained essentially unchanged.

Thus, after a single intra-amniotic injection of 500 mg. of hydrocortisone sodium succinate the following were noted: (1) estriol values declined in all three compartments; (2) cortisol was rapidly increased in the maternal compartment, but returns to normal levels at the time of cesarean section in maternal and umbilical vein cord plasma while remaining elevated in the amniotic compartment; (3) progesterone was increased in the fetal and amniotic compartments; but remained essentially unchanged in the maternal compartment; (4) the foam test was constantly improved in the direction of an intermediary or positive test and the quantitative lecithin-sphingomyelin values were increased by almost twofold; (5) in our series, none of the infants developed a respiratory distress syndrome nor has any difficulty with the first breath or the Apgar score. No low-birth-weight babies were delivered and the creatinine values were even improved by the injection.

When cortisol is injected in the amniotic fluid, the fetus will swallow and introduce it into the fetal circulation by digestive absorption.[17] This absorption will be followed by dissemination within the fetus and transplacental passage, where it will finally reach the maternal circulation.[17] When injected, hydrocortisone

Table II. Estriol, cortisol, and progesterone in amniotic fluid

Case No.	Estriol (μg/100 ml.)		Cortisol (μg/100 ml.)		Progesterone (ng./ml.)	
	Before	48 hr. after	Before	48 hr. after	Before	48 hr. after
1	100	—	—	—	46.2	—
2	65.0	66.3	5.8	65.2	3.8	86.0
3	13.0	7.0	3.1	49.4	19.0	52.0
4	105.0	51.0	6.2	31.5	31.2	83.0
5	39.6	28.0	6.7	33.5	39.6	51.2
6	189.0	115.0	7.3	41.3	27.6	44.8
7	50.0	12.7	5.0	34.3	15.2	130.0
8	58.0	—	4.0	49.5	16.0	24.0
9	121.0	99.0	6.4	30.2	5.2	24.0
Mean	82.3	47.4	5.5	41.9	22.6	61.9

Table III. Quantitative lecithin, foam test, and creatinine values in amniotic fluid, birth weight, and Apgar values

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9
Quantitative lecithin (μM):									
Before	—	—	—	—	—	201.8	69.4	190.0	178.0
48 hr. after	—	—	—	—	—	201.8	121.0	383.0	271.2
Foam test:									
Before	Neg.	Inter.	Neg.	Inter.	Inter.	Inter.	Neg.	Inter.	Posit.
48 hr. after	Inter.	Posit.	Inter.	Posit.	Posit.	Posit.	Inter.	Posit.	Posit.
Creatinine (mg./100 ml.):									
Before	2.8	3.0	1.2	3.0	2.2	2.2	1.0	2.2	2.4
48 hr. after	3.0	3.6	1.8	2.0	2.3	3.0	1.5	2.4	2.5
Birth weight (Gm.)	3,320	3,205	2,980	3,660	2,950	4,813	2,950	2,650	3,250
Apgar score	6-9	7-10	9-10	9	9	8-10	7-10	8-10	9-10

Table IV. Estriol, cortisol, and progesterone values in maternal plasma

Case No.	Estriol (μg/100 ml.)			Cortisol (μg/100 ml.)			Progesterone (ng./ml.)		
	Before	After		Before	After		Before	After	
		24 hr.	48 hr.		24 hr.	48 hr.		24 hr.	48 hr.
1	22.0	3.3	—	38.8	74.8	25.7	147.6	—	157.2
2	11.8	4.6	1.8	30.5	70.4	28.7	141.6	136.8	145.2
3	8.8	3.7	2.1	31.7	91.5	32.9	99.0	90.0	74.0
4	6.0	2.5	2.2	19.1	43.8	25.8	94.4	79.0	36.4
5	—	—	—	—	—	—	—	—	—
6	25.0	7.8	4.1	29.0	142.5	39.9	130.0	118.0	86.0
7	10.0	1.8	1.8	25.7	164.4	34.2	108.0	82.0	114.0
8	9.5	1.8	1.8	20.5	157.2	29.5	51.6	52.4	34.4
9	13.6	1.3	1.3	26.9	128.4	50.2	72.0	40.8	55.2
Mean	13.5	3.3	2.2	27.9	109.1	33.4	93.0	85.6	87.8

Table V. Estriol, cortisol, and progesterone values of venous plasma in umbilical cord

	No. 1	No. 4	No. 6	No. 7	No. 8	No. 9	Mean value	Normal values
Estriol (μg/100 ml.)	31.0	23.5	17.1	16.6	8.5	6.5	17.2	79.0 ± 25.0
Cortisol (μg/100 ml.)	26.3	23.6	16.6	22.8	18.7	19.7	21.3	18.7 ± 5.6 (10)
Progesterone (ng./ml.)	632	1440	248	352	120	194.4	497.6	109.1 ± 38.6

sodium succinate is rapidly hydrolyzed to yield mainly free cortisol and associated metabolites within the fetus. However, we were able to observe an increased cortisol value in all compartments. In the maternal compartment, in a case not included in the present series, we were able to determine a progressive rise within 4 hours after injection, the peak was reached at 20 hours after injection, and the decrement was noticed 28 hours after injection. Since we did not use a chromatographic separation it is also probable that other glycocorticoids as well as our hydrolyzed hydrocortisone were measured by our method.

It is probable that the hydrocortisone given intra-amniotically reached the fetus in a highly biologically active form because it had only to be hydrolized. The amount of hydrocortisone injected is probably too high a dose because it depressed maternal and fetal estriol values. Estriol suppression by maternal adrenocorticotropic hormone injection[18, 19] has been previously reported. By intra-amniotic injection of cortisol we were able to depress estriol values not only in fetal plasma but also in amniotic fluid and maternal plasma. In a special case, we did two injections of hydrocortisone, the first one at 35 weeks and the second one at 38 weeks. In this case, we were able to determine that maternal plasma estriol had already returned to normal values 72 hours after injection. The suppression of estriol is therefore reversible, of short duration, and should be weighted against the advantages gained by the increase in lecithin-sphingomyelin content.

As previously noticed by Giannopoulos and associates,[20] there are specific pulmonary receptors in animals for glucocorticoids. In our patients, we noticed a qualitative change in the L/S ratio following the intra-amniotic injection of hydrocortisone. We were also able to observe a quantitative change following injections. This change was surprising in the observed case of positive foam test. This small group of hydrocortisone-treated patients and control subjects has confirmed the value of the foam test (FT) as a screening test because none of the intermediate or positive FT has developed respiratory distress syndrome.

Finally, quite contrary to animal studies,[21] in which a decline in maternal progesterone followed fetal infusion of ACTH, we did not observe such maternal changes in progesterone values. However, we did observe increased values of progesterone in the fetal and intra-amniotic compartments. The same observations were made in a case of anencephaly[22] and seem to confirm an earlier report[23] that maternal cholesterol is the major precursor of placental progesterone whereas fetal cholesterol is a very efficient precursor of fetal steroids in the biosynthesis of estriol in the human term placenta. It is probable that progesterone increases on the fetal and amniotic side because there is a decreased utilization of precursors for the biosynthesis of estriol and cortisol. It is also possible, however, that progesterone and cortisol (injected) will compete for the CBG located in the myometrium and therefore increase temporarily the values of one or the other.[24]

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Bioerodible
Polymers



Oral Osmotic
Delivery System

Alza is the only company devoted entirely to the optimization of drug therapy through the development of Therapeutic Systems. These "Systems" are vehicles for precision drug delivery with minimal physiologic disturbances and minimal reliance on patient compliance.



Ocular
Therapeutic System

alza

THE THERAPEUTIC SYSTEMS COMPANY

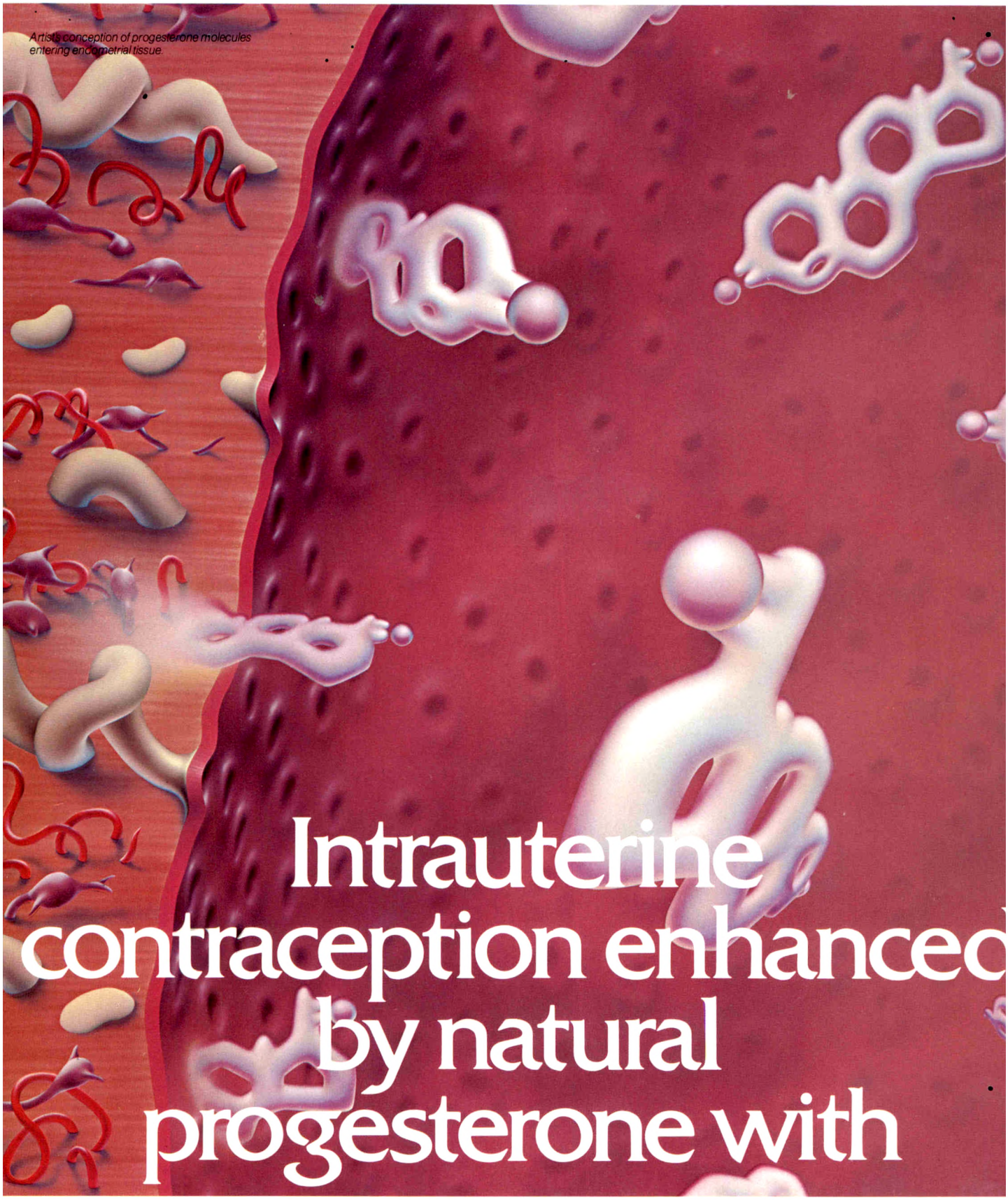


Transdermal
Therapeutic System

Alza is different from the ordinary pharmaceutical company in that it is not involved in manipulating or developing the architecture of existing drug molecules. Alza is the Therapeutic Systems Company.



Liquid Infusion
System



Intrauterine contraception enhanced by natural progesterone with

no systemic hormonal effects*

The Progestasert® System is a new approach to intrauterine contraception.

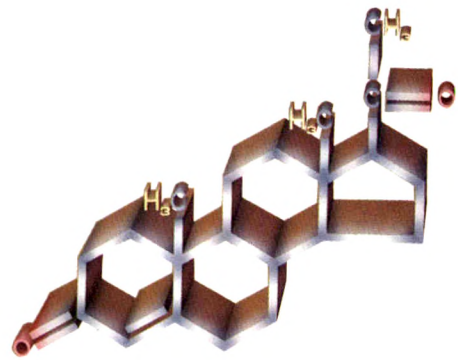
The natural ovarian hormone progesterone is placed to act continuously directly within the target organ — the uterus. Thus, only minute quantities of this rapidly catabolized hormone are needed.

Hormonally enhanced contraception is achieved in utero without systemic side effects* and without affecting the hypothalamic-pituitary-ovarian axis. Effective contraception is achieved for a full year from a single Progestasert® System placement.

Alza introduces Progestasert®

Intrauterine Progesterone Contraceptive System

Contraceptive efficacy of the Progestasert® System enhanced by progesterone



WHY PROGESTERONE?

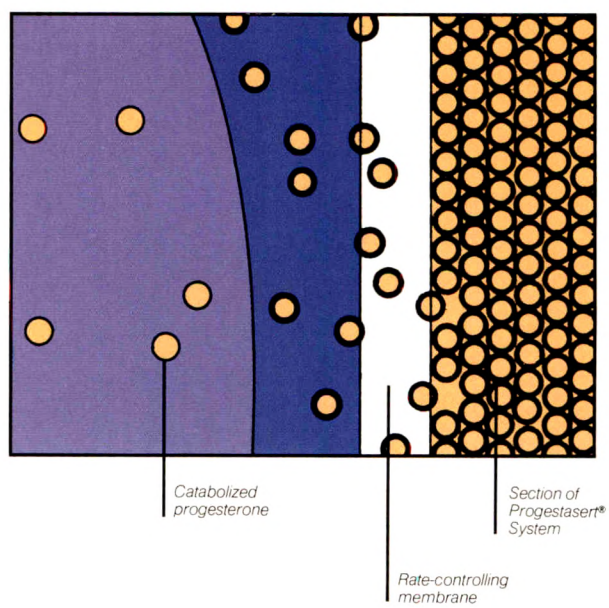
Progesterone—pregn-4-ene-3,20-dione ($C_{21}H_{30}O_2$)—is a naturally occurring female hormone, produced by the corpus luteum, adrenal cortex and placenta.

Progesterone is the contraceptive agent of choice for the Progestasert® System because:

- ☐ it is endogenous to the endometrium
- ☐ it has a short metabolic half-life
- ☐ it enhances the contraceptive effect at low concentrations when administered locally to the uterus
- ☐ it is rapidly catabolized by the endometrium
- ☐ it permits continuation of ovulation and, therefore, the length of the menstrual cycle is unaltered
- ☐ its effect on the endometrium reverses rapidly upon removal of the Progestasert® System.

CONTINUOUS MICRODOSAGE OF PROGESTERONE

The total quantity of progesterone contained in one Progestasert® System for one year's use is only 38 mg—less than the amount produced in one day by the corpus luteum during the latter part of the menstrual cycle. The amount of progesterone released daily from the System corresponds to a small percentage of the daily physiologic production.



A unique drug delivery system

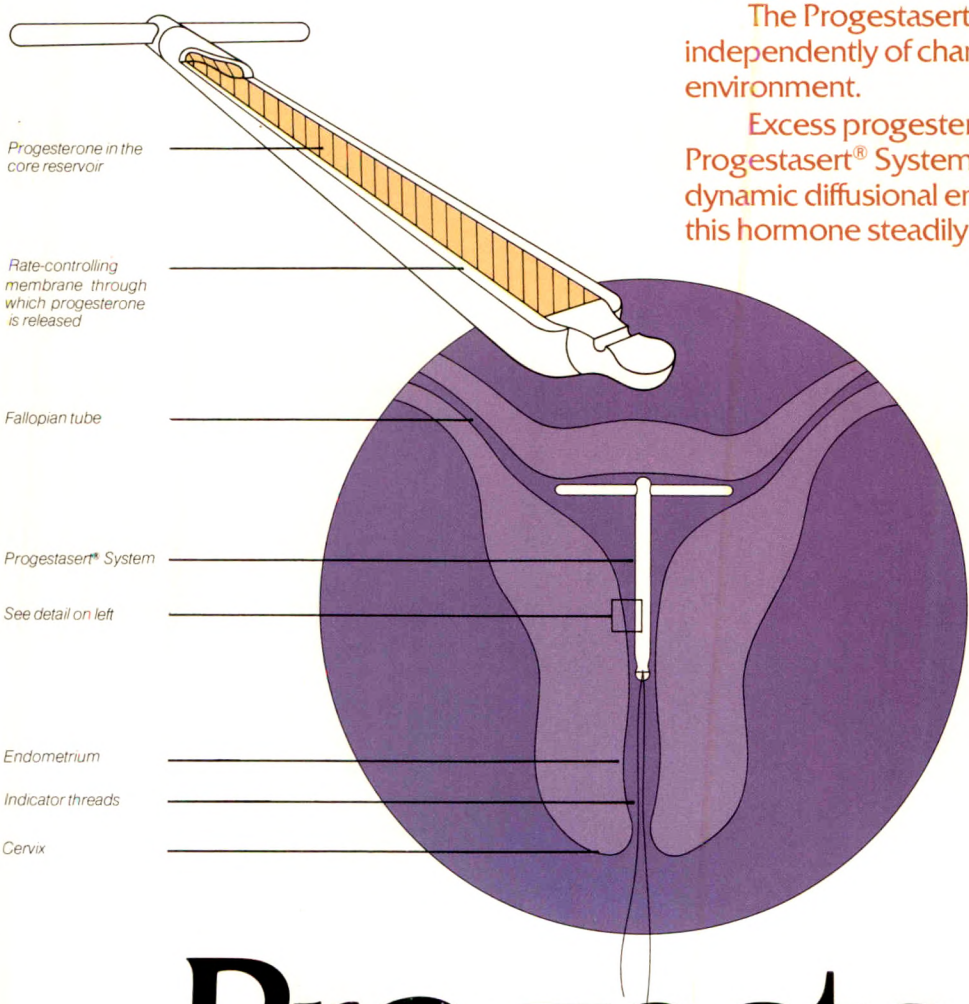
The Progestasert® System is a diffusional system designed to deliver microquantities of progesterone. The two key components are:

- ☐ a core reservoir of progesterone crystals with barium sulfate (for radiopacity) in medical-grade silicone oil
- ☐ an inert diffusional membrane of ethylene/vinyl acetate copolymer that surrounds the core reservoir and provides programmed control of progesterone release

When the Progestasert® System is placed in the uterine environment, progesterone molecules diffuse through the membrane into the uterine lumen at the average rate of 65 micrograms per day for one year.

The Progestasert® System functions independently of changes in the uterine environment.

Excess progesterone within the Progestasert® System provides the thermodynamic diffusional energy needed to release this hormone steadily for an entire year.



WHY THE T CONFIGURATION?

A T-shaped configuration was selected to contain the progesterone reservoir because this configuration has shown:*

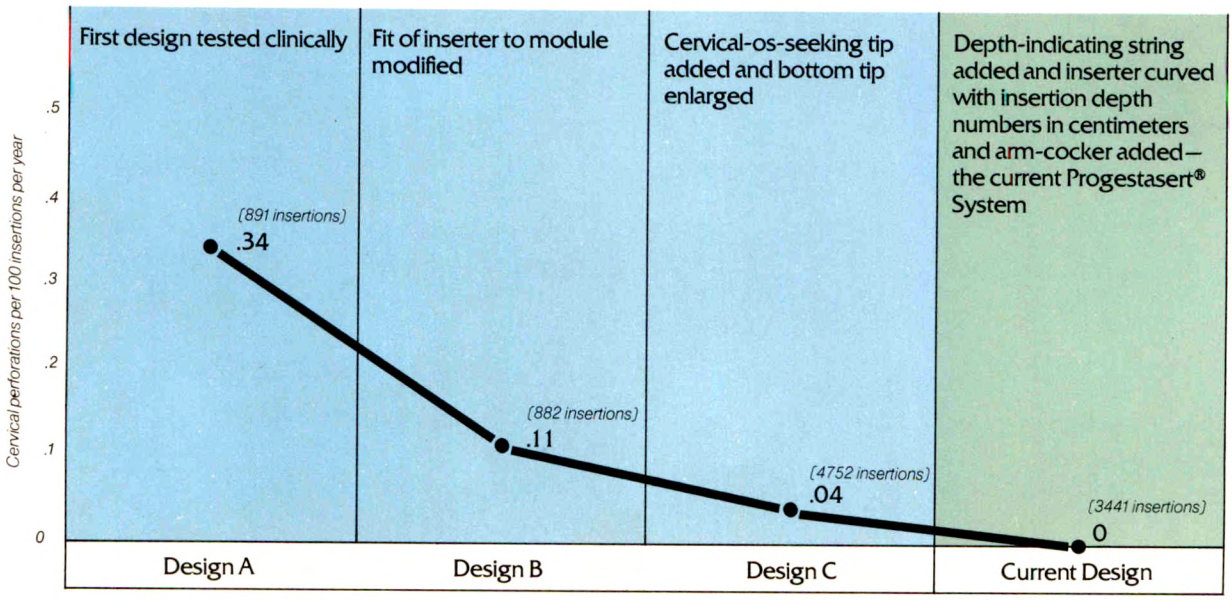
- ☐ easy insertion
- ☐ excellent retention by the uterus
- ☐ minimal symptomatic evidence of uterine irritation
- ☐ easy removal

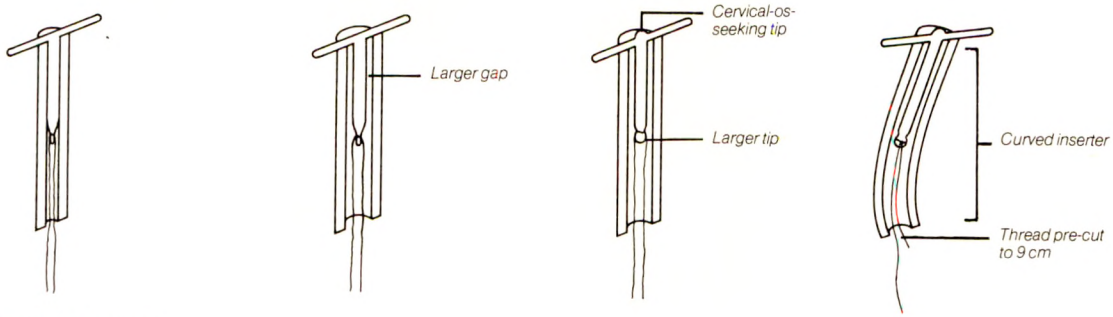
*Tatum HJ: Intrauterine Contraception. American Journal of Obstetrics and Gynecology, 112: 1000, 1972.

Progestasert®

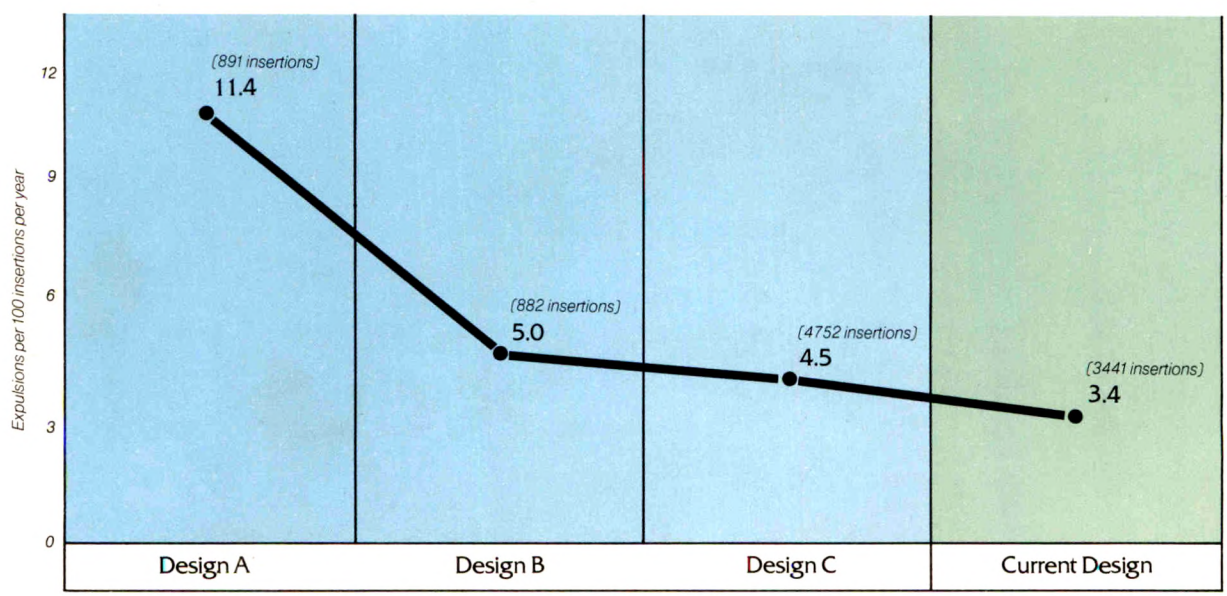
Intrauterine Progesterone Contraceptive System

CERVICAL PERFORATIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED





EXPULSIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED



These graphs do not represent a comparison of inserters produced by different manufacturers. Rather, they depict stages in ALZA's development of the Progestasert® System inserter.

All numbers are expressed as events per 100 women per year.

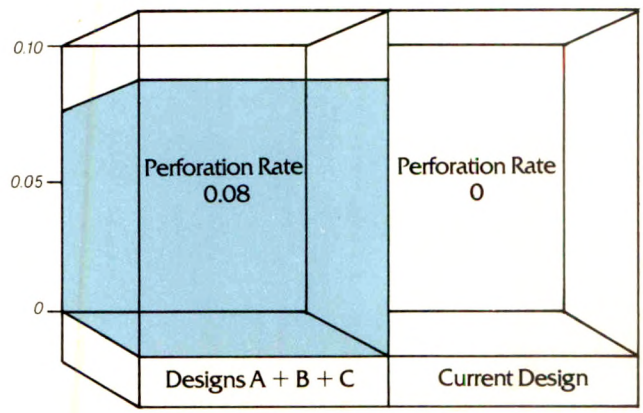
Inserter designed for safety and effective placement

As recently noted by Mishell, inserter design is increasingly recognized as important to the efficacy and safety of intrauterine contraceptive devices. "Proper placement... is of extreme importance for IUD effectiveness... (Thus), more attention should be directed toward the development of optimal IUD inserters than to changes in the IUD design."*

Some untoward effects with intrauterine devices— such as perforation and expulsion— in the past have been due to difficulties in placement. Since the technique of insertion and correct high fundal positioning play an important role in assuring contraceptive effectiveness and patient comfort and safety, much attention has been directed toward the development of the Progestasert® System inserter.

In controlled studies, evolutionary changes in the inserter and the Progestasert® System have demonstrated a decrease in the incidence of expulsions, cervical perforations, and uterine perforations which have paralleled these design changes. The incidence for both cervical and uterine perforations has decreased to the point that neither type of perforation has occurred with the 3,441 insertions with the final design after an average of more than nine months of exposure for these women.

UTERINE PERFORATIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED



While these data reflect the importance of the design changes, the lack of perforations during these limited trials in no way suggests the Progestasert® System and its inserter will be trouble-free in general use. Perforations, both cervical and uterine, may occur with the Progestasert® System as its use becomes more widespread. The rate of perforation will depend upon anatomical and physiological variations of the women receiving the System and the care taken during the insertion process.

Progestasert®

Intrauterine Progesterone Contraceptive System

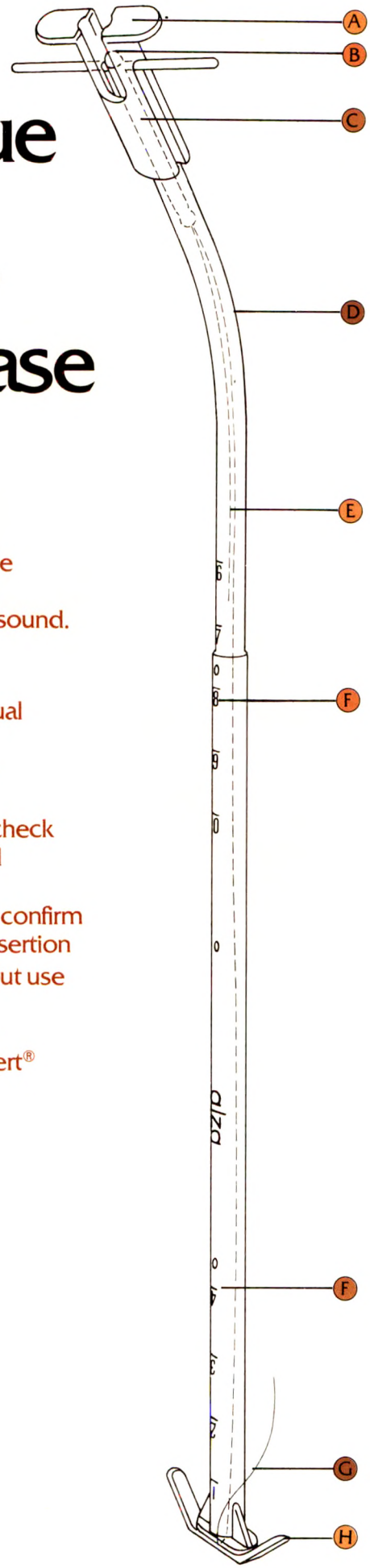
The System and its unique inserter-designed for safety and ease of insertion

The Progestasert® System inserter facilitates correct System placement while minimizing the risk of perforation, and is designed to function much like a uterine sound.

Features of the inserter:

- ☐ pre-curvature to facilitate insertion
- ☐ malleability for adapting to the individual uterus
- ☐ dual checking mechanism for correct placement
  - — centimeter markings on inserter to check conformity with previously sounded uterine depth
  - — indicator thread length designed to confirm proper System position following insertion
- ☐ high fundal placement achieved without use of plunger or push-rod

Comprehensive illustrated insertion instructions are a part of every Progestasert® System package.



Actual Size



A. Arm-cocker allows the arms of the T to be folded aseptically, using one-handed technique just prior to insertion.

B. Cervical-os-seeking tip helps guide the System into the cervical canal, making insertion easier and more comfortable.

C. Vertical stem of the System designed with flexibility and rounded tip to minimize cervical perforation risk.

D. Curved portion of inserter designed to conform to anatomic configuration of most cervical-uterine cavities. Malleability allows accomodation to variations in uterine anatomy.

E. Indicator monofilament thread, extended 9 cm from the top of the System, verifies correct placement at insertion.

F. Graduations (in centimeters) to determine uterine position and depth, and to confirm correct System placement.

G. Retainer monofilament thread extends the length of the inserter and is anchored by the thread-retaining plug to retain the System in the inserter.

H. Thread-retaining plug is removed to release the System in the uterus.

Safety studies

Clinical safety studies demonstrated:

- ☐ No extrauterine metabolic or endocrine effects in humans*
- ☐ Endometrial changes induced by the Progestasert® System disappear within weeks after System removal
- ☐ Rapid return to fertility confirmed in women discontinuing use of the Progestasert® System in the hope of becoming pregnant. The cumulative conception rate among 154 women was 49 per 100 women pregnant at 3 months after removal, and 76 per 100 women at 12 months after removal. These rates of return to fertility are similar to those reported following removal of an IUD.

Effective contraception for one year from a single placement

The Progestasert® System functions unattended for one year at a continuous release rate of 65 micrograms of progesterone per day, eliminating reliance on daily hormone administration.

Yearly removal and placement can coincide with annual visits for physical examination and Pap smear, as encouraged by the American College of Obstetrics and Gynecology. (Currently accepted practice used by recognized authorities, reported in ACOG Technical Bulletin #29, February, 1975, p 7.)

Progestasert®

Intrauterine Progesterone Contraceptive System

Some clinical aspects

Data were collected in 40 clinics involving 5,495 women over a period of 45,848 woman-months. These trials were designed to obtain data that would predict the true use-effectiveness of the System.

HIGHLY EFFECTIVE INTRAUTERINE CONTRACEPTION

Clinical results have demonstrated pregnancy rates of 1.9† in parous patients and 2.5† in nulliparous patients. A similar T-shaped unit, but without progesterone in the stem, produced a pregnancy rate of 18.3†.

HIGH DEGREE OF ACCEPTABILITY

Clinical studies have demonstrated a high continuation rate. Approximately 8 of every 10 parous and 7 of every 10 nulliparous women continued use of the Progestasert® System for a full year.

SHAPE PROVIDES EXCELLENT RETENTION

Expulsion rates of 3.1† and 7.5† were observed for parous and nulliparous women respectively.

INSERTER PROVIDES SAFE PLACEMENT

No uterine perforations have occurred with 3,441 insertions using the current pre-curved, malleable inserter during controlled clinical trials. This should not be interpreted as a guarantee that perforations will not occur with the Progestasert® System.

	Parous	Nulliparous
PREGNANCY RATE	1.9	2.5
EXPULSIONS	3.1	7.5
CONTINUATION RATE	79.1	70.9

Features and benefits

- ☐ Contraception provided by progesterone, identical to the natural ovarian hormone
- ☐ No known systemic hormonal effects*
- ☐ Continuous delivery of progesterone in microgram amounts/day
- ☐ Effective contraception for one year from one System placement
- ☐ High degree of patient acceptability
- ☐ Excellent uterine retention
- ☐ Minimal reliance on patient compliance during its year of use when compared to extrauterine contraceptives
- ☐ Prompt return to pre-insertion fertility following System removal
- ☐ Inserter designed for safety and ease of insertion

Candidates for the Progestasert® System

THE NEW CONTRACEPTIVE USER

The natural progesterone contraception provided by the Progestasert® System without systemic hormonal effects, along with minimal dependence on patient compliance, small unit size, and easy insertion, make the Progestasert® System an attractive first contraceptive for many women.

THE NONCOMPLIER

The daily regimen of pill-taking proves beyond the capability of some patients for whom hormonal contraception is preferable. The Progestasert® System reduces requirements for patient compliance to once-a-year replacement.

THE PATIENT DISCONTINUING ORAL CONTRACEPTIVES

Patient-initiated— the Progestasert® System offers the opportunity to continue hormonally enhanced contraception without the adverse systemic hormonal effects* that cause many women to dicontinue oral contraceptives.

Physician-initiated— some physicians consider it important for the patient to discontinue oral contraceptive use until the body regains its normal hormonal balance. Some physicians discontinue the Pill permanently. Recent studies strongly suggest that oral contraceptive users are at greater risk of developing coronary thrombosis than nonusers. The Progestasert® System, with its lack of adverse systemic hormonal effects,* can be the desired alternative contraceptive for former users of the Pill.

THE PATIENT DISCONTINUING OTHER CONTRACEPTIVE METHODS

The inconvenience and lower efficacy rates of diaphragms and condoms make the Progestasert® System an attractive alternative for the patient desiring intrauterine hormonal contraception without systemic hormonal effects.*

THE IUD PATIENT DUE FOR REINSERTION

For those patients already using some form of intrauterine contraception, the Progestasert® System, designed for safety, offers an effective alternative to their present IUD and may be considered at reinsertion time.



Progestasert®

Intrauterine Progesterone Contraceptive System

Ordering Information

IF YOU WOULD LIKE FURTHER INFORMATION ABOUT ALZA, THERAPEUTIC SYSTEMS, THE PROGESTASERT® SYSTEM, DETAILED INSERTION INSTRUCTIONS OR WOULD LIKE TO ORDER PROGESTASERT® SYSTEMS FOR YOUR PRACTICE, CALL THE FOLLOWING TOLL-FREE NUMBER: (800) 227-9953 OR WRITE TO ALZA PHARMACEUTICALS, 3170 PORTER DRIVE, PALO ALTO, CALIFORNIA 94304.

Progestasert®

Intrauterine Progesterone Contraceptive System

Release rated 65 μg/day progesterone for one year.

DESCRIPTION

The Progestasert® Intrauterine Progesterone Contraceptive System is a white, T-shaped unit constructed of ethylene/vinyl acetate copolymer (EVA) containing titanium dioxide. The 36 mm tubular vertical stem of the T contains a reservoir of 38 mg of progesterone, USP, together with barium sulfate, USP, for radiopacity; both are dispersed in medical grade silicone oil. The 32 mm horizontal crossarms are solid EVA. Two monofilament nylon indicator/retrieval threads are fastened to the base of the T stem. The Progestasert® system is packaged sterile within its curved, malleable inserter. Progesterone is released from the system at an average rate of 65 μg/day for one year by membrane-controlled diffusion from the reservoir. None of the inert ingredients of the reservoir or membrane—barium sulfate, silicone oil, titanium dioxide, or EVA—is released from the system.

ACTION

Available data indicate that the contraceptive effectiveness of the Progestasert® system is enhanced by its continuous release of progesterone at an average rate of 65 μg/day into the uterine cavity. The mechanism by which progesterone enhances the contraceptive effectiveness of the T is local, not systemic. The concentration of luteinizing hormone, estradiol, and progesterone in systemic venous plasma follow regular cyclic patterns indicative of ovulation during use of the Progestasert® system. Blood chemistry studies related to liver, kidney, and thyroid function also reveal no changes.

During use of the system, the endometrium shows progestational influence. Following removal of the system, the endometrium rapidly returns to its normal cyclic pattern and can support pregnancy. The local mechanism by which continuously released progesterone enhances the contraceptive effectiveness of the T has not been conclusively demonstrated. The hypotheses that have been offered are: progesterone-induced inhibition of sperm capacitation or survival, and alteration of the uterine milieu so as to prevent nidation.

INDICATION

The Progestasert® system is indicated for contraception.

CONTRAINDICATIONS

Pregnancy or suspicion of pregnancy; abnormalities of the uterine cavity; acute pelvic inflammatory disease or history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past 3 months; uterine or cervical malignancy; unexplained genital bleeding until suspicion of cancer is ruled out; acute cervicitis.

WARNINGS

A. Pregnancy

1. Septic abortion. Recent reports have indicated an increased incidence of septic abortion, associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an intrauterine device (IUD) in place. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Progestasert® system in situ, it should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the system remains in situ, she shall be warned of the increased risk of sepsis and be followed with close vigilance.
2. Congenital anomalies. Systemically administered sex steroids, including synthetic progestational agents, have been associated with an increased risk of congenital anomalies including cardiovascular anomalies. Such effects have not been reported with progesterone itself, which is produced in large concentrations during pregnancy.
3. Ectopic pregnancy. A pregnancy that occurs while a patient is wearing an IUD is much more likely to be ectopic in nature. Therefore, such patients in whom pregnancy occurs should be carefully evaluated.

B. Severe Pelvic Infection

Occasionally serious pelvic infection may occur with an IUD in situ. Under such circumstances the IUD should be removed, appropriate bacteriological studies done, and appropriate antibiotic treatment instituted.

C. Perforation

Perforation of the uterus may occur. If this occurs, the device should be removed. Local inflammatory reaction with abscess formation is a possibility if an IUD is left in the abdomen. Cervical perforation, often asymptomatic, has also been reported. If such occurs, the device should be removed.

PRECAUTIONS AND ROUTINE EXAMINATIONS

A. Patient Examination

The physician should make a determination that the patient is not pregnant. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed during or shortly following a menstrual period. The system should not be inserted postpartum or postabortion until involution of the uterus has been completed. Prior to insertion, a pelvic examination, pap smear, and gonorrhea culture should be done. Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The patient should be told that some bleeding or cramps may occur during the first few days after insertion. If these symptoms continue or are severe, she should report to her physician. She should be cautioned not to pull on the threads, which would displace the system.

B. Requirements for Continuation and Removal

The Progestasert® system must be replaced each year. There is no evidence of decreasing contraceptive efficacy with time before one year, but the contraceptive effectiveness of the Progestasert® system after one year has yet to be established. Therefore, the patient should be informed of the known duration of the contraceptive efficacy and be advised to return in one year for re-examination, removal and possible reinsertion.

The Progestasert® system should be removed for the following medical reasons: Menorrhagia and/or metrorrhagia producing anemia; uncontrolled pelvic infection; intractable pain, often aggravated by intercourse; pregnancy, if the thread is visible; uterine or cervical malignancy; uterine or cervical perforation; an increase in length of thread extending from the cervix, or any other indication of partial system expulsion.

C. Continuing Care of Patients Using the Progestasert® System

Patients should be re-examined and evaluated within three months after Progestasert® system insertion. Routine annual examination, removal of the Progestasert® system, and reinsertion of a new Progestasert® system along with appropriate medical and laboratory evaluation should be carried out.

ADVERSE REACTIONS

Reported adverse reactions include: Endometritis, spontaneous abortion, septic abortion, septicemia, perforation of uterus and cervix, pelvic infection, cystic masses in pelvis, abdominal adhesions, intestinal obstruction, cervical erosion, vaginitis, leukorrhea, cystitis, pregnancy, ectopic pregnancy, uterine embedment, difficult removal, complete or partial expulsion, intermenstrual spotting, prolongation of menstrual flow, anemia, amenorrhea or delayed menses, pain and cramping, backaches, dyspareunia, leg pain or soreness, weight loss or gain, nervousness, bradycardia and syncope secondary to insertional pain.

DOSAGE AND ADMINISTRATION

A single Progestasert® system is to be inserted into the uterine cavity (see Precautions section). Present information indicates that the contraceptive effectiveness of the system is retained for one year and the system must be replaced one year after insertion.

HOW SUPPLIED

Available in cartons containing six sterile systems (Progestasert® system with an inserter).

CLINICAL STUDIES

Different event rates have been recorded with the use of different contraceptive methods. Inasmuch as these results are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and do not discontinue due to adverse reactions or pregnancy. In clinical trials sponsored by Alza with the Progestasert® system, use-effectiveness was determined for parous and nulliparous women by the life table method. (Rates are expressed as events per 100 women through 12 months of use.) This experience is based on 45,848 woman-months of use with 5,495 women, of whom about 25% were nulliparous; 2,157 women completed 12 months of use.

	Parous	*Nulliparous*
Pregnancy	1.9	2.5
Expulsion	3.1	7.5
Medical Removals	12.3	16.4
Continuation Rate	79.1	70.9

CAUTION

Federal law prohibits dispensing without prescription.

alza

OBSTETRICS

Phosphatidylinositol and phosphatidylglycerol in amniotic fluid: Indices of lung maturity

MIKKO HALLMAN, M.D.
MARIE KULOVICH
ELSA KIRKPATRICK
ROBERT G. SUGARMAN, M.D.*
LOUIS GLUCK, M.D.
La Jolla and Los Angeles, California

The minor phospholipids in amniotic fluid from normal pregnancies were correlated with the well-established index of lung maturity, the lecithin/sphingomyelin (L/S) ratio. When the L/S ratio was less than 1.0, the acidic phospholipids phosphatidylglycerol (PG) and phosphatidylinositol (PI) were absent or low in concentration (0.0 to 2.5 per cent of lipid phosphorus). Parallel to the increase in the L/S ratio to 2.0, the content of PI increased to 6.0 to 8.5 per cent of lipid phosphorus. PG, the unique phospholipid of lung surfactant, first appeared and PI concomitantly decreased when the L/S ratio exceeded 2.0, indicating the secretion of mature lung surfactant. Analysis of PI and PG in amniotic fluid as markers of surfactant seems to be of value as an additional index of prenatal evaluation of lung maturity and may be particularly useful when the specimen is contaminated with blood.

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A preliminary report was presented at the Eighth Annual Meeting of the Society for the Study of Reproduction, Ft. Collins, Colorado, July, 1975.

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THE LECITHIN/SPHINGOMYELIN (L/S) ratio in amniotic fluid is a widely accepted test for pulmonary maturity of the fetus to prevent the respiratory distress syndrome (RDS) of the newborn infant.[1–5] The bases of the L/S ratio are: first, that there is deficient surfactant in RDS[6, 7]; second, that secretion of fetal lung fluid containing surfactant contributes to amniotic fluid[8, 9]; third, that the biosynthesis of surfactant lecithin matures at about 35 weeks' gestation in the normally developing fetal lung.[7]

The surfactant complex lines alveoli and reduces surface tension on expiration. Thus, the acini are stabilized. Nearly 85 per cent of surfactant is phospholipid which, unlike other body phospholipids, contains highly saturated fatty acids.[10]

Lecithin contributes nearly 80 per cent of the surfactant phospholipids. Other minor components

Table I. The molar contents of phospholipids in amniotic fluid as percentages of total lipid phosphorus

Phospholipid	*Category 1: PI + PG, <4.0; PG, <0.5; L/S ratio,* 0.65 ± 0.37; 25 samples*	*Category 2: PI + PG, ≥4.0; PG, <0.5; L/S ratio,* 1.95 ± 0.43; 18 samples*	*Category 3: PI + PG, ≥4.0; PG, ≥0.5; L/S ratio,* 7.00 ± 4.12; 23 samples*
PI	1.5 ± 1.2	7.2 ± 1.8	5.3 ± 1.7
PG	0.0 ± 0.1	0.1 ± 0.1	5.2 ± 2.5
Phosphatidylethanolamine	7.8 ± 0.8	6.5 + 1.0	3.7 ± 1.1
Phosphatidylserine	5.0 ± 0.9	4.0 ± 0.8	2.1 ± 0.5
Lecithin	52.0 ± 6.0	65.7 ± 5.8	76.2 ± 3.0
Sphingomyelin	31.4 ± 6.8	15.2 ± 5.0	5.7 ± 2.9
Total	97.7 ± 1.0	98.7 ± 1.4	98.2 ± 1.4

*From acetone-precipitable fraction by reflectance densitometry. Mean ± S.D.

include phosphatidylinositol (PI), phosphatidylethanolamine, sphingomyelin, and phosphatidylserine. The second major phospholipid is phosphatidylglycerol (PG), comprising more than 10 per cent of surfactant phospholipids in the adult.[11, 12] Animal structures other than surfactant contain only traces of this phospholipid.

Studies on the perinatal development of lung surfactant in the rabbit revealed that in the preterm fetus PG was absent and PI was unusually prominent. Thereafter, PG appeared and PI concomitantly decreased.[13] The present report is a study showing similar development in the human subject and correlates PI and PG with the functional maturity of the lung.

Material and methods

Sixty-six amniotic fluid specimens from 44 women were obtained by transabdominal amniocentesis strictly for maternal and/or fetal indications. Cases of maternal diabetes mellitus and hypertensive diseases were not included. None of the mothers received corticosteroid derivatives.

Each amniotic fluid specimen of 5 ml. or more was centrifuged at 800 × g for five minutes. The lipid extract derived from the supernatant was divided into two parts. In one part, one L/S ratio and the per cent of total lecithin that precipitated in cold acetone were measured by reflectance densitometry on thin-layer plates of silica gel H containing 5 per cent $(NH_4)_2SO_4$ as described by Gluck and associates.[14] The other part was analyzed for phospholipids with plain silica gel H plates. To increase the resolution of individual components, thin-layer chromatograms were developed twice, each time in a different dimension. The solvents used in two-dimensional chromatography were as follows: first solvent system, (1) tetrahydrofuran-methylal-methanol-2N NH_4OH (10-3-2-1.1, v/v) and (2) chloroform-methanol-H_2O (65-25-4, v/v); second solvent system, (1) chloroform-methanol-58 per cent NH_4OH-H_2O (130-60-5-4, v/v) and (2) chloroform-methanol-acetic acid-H_2O (160-50-12-4, v/v). A simplified solvent system developed by R. Bustos and M. V. Kulovich occasionally was used. Between the individual runs, the plates were heated at 70° C. for five minutes. After the development of the chromatograms and the visualization with iodine, the phospholipid phosphorus was measured by a modification[13] of the Bartlett method.

Results

The molar contents of individual phospholipids were expressed as percentages of total phospholipid. The actual concentrations of individual phospholipids in amniotic fluid also were calculated, but the scatter of the results was considerable (data not shown). This may be due to individual variation in amniotic fluid volume, a factor that is obviated when the results are expressed on the basis of total phospholipid.

The phospholipids analyzed were PI, PG, phosphatidylethanolamine, phosphatidylserine, lecithin and sphingomyelin. In addition, some other phospholipids could be identified. However, their content totaled 3.5 per cent or less of total phospholipid phosphorus.

In 20 of 44 cases, samples were obtained within 72 hours prior to birth. Of these, 15 had an L/S ratio of 2 or more and no RDS when born. Of the five with L/S ratios less than 2.0, four had RDS. The parameters measured were correlated to either L/S ratio or per cent of acetone precipitable over total lecithin.

The material was divided into three categories on the basis of PI and PG content (Table I). In the first, PI concentration was less than 4 per cent of total phospholipid and PG was practically absent. In this category, L/S ratios were low, exceeding 1 in only three of 24 cases. In the second, more than 4 per cent PI was

present and PG was less than 0.5 per cent. Here, L/S ratios were transitional or mature (lowest value, 1.0; highest, 3.1). In the third category, the specimens had both PG and PI. Here, L/S ratios always were mature. The changes in concentrations of phosphatidylethanolamine and phosphatidylserine were less marked except in the third group where their contents were significantly less than in the two other groups.

Fig. 1 shows concentrations of PI as a function of the L/S ratio. The contents increased with an increasing L/S ratio up to 3. Thereafter, PI levels gradually fell. Fourth-degree regression analysis showed a significant correlation with an r value of 0.860. At an L/S ratio of 2, the most likely PI content was 7.2 per cent of lipid phosphorus.

The relationship between PG and the L/S ratio is illustrated in Fig. 2. With an L/S ratio less than 2, PG was practically absent. As the L/S ratio increased, PG appeared. Linear regression analysis showed a significant correlation with an r value of 0.873.

The sum of PI and PG correlated with the L/S ratio (data not shown). The sum increased sharply until the L/S ratio reached the value of 3. Thereafter, the increase was small despite increasing amounts of PG due to the simultaneous decrease in PI. Third-degree regression analysis revealed a remarkably good correlation between the L/S ratio and these acidic phospholipids with an r value of 0.953.

Contents of PI and PG in amniotic fluid during normal pregnancy are shown in Fig. 3. After 30 weeks, PI increases, peaks at 36 to 37 weeks, then gradually decreases. PG appears after 35 weeks' gestation and continues to increase beyond term.

Fig. 4 describes the L/S ratio, the PG/PI ratio, and the sum of PI and PG as a function of gestational age. The sum of these acidic phospholipids has been expressed on the basis of phosphatidylethanolamine rather than total phospholipid. Phosphatidylserine and sphingomyelin also could be used as reference compounds, similar to phosphatidylethanolamine (data not shown).

The sum of PI and PG (divided by phosphatidylethanolamine) increases parallel with the L/S ratio, exceeding 1 at an L/S ratio of 2. The PG/PI ratio starts to increase after 35 weeks of gestation. At term, it exceeds 1 and three weeks later approaches or exceeds 3.

Comment

The present study demonstrates the stepwise appearance of PI and PG in amniotic fluid during the last trimester of normal pregnancy. Studies on lung effluent of newborn babies[15] and the isolated surfactant complex from perinatal rabbits[13] indicate an analogous

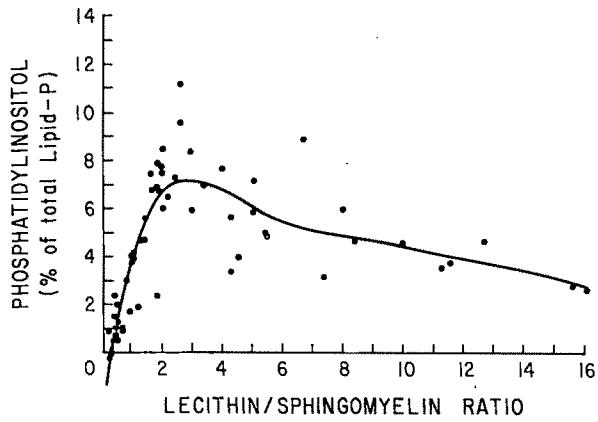


Fig. 1. Relationship between densitometrically measured L/S ratios from acetone-precipitable fractions and PI content as determined by phosphorus *(P)* analyses. Fourth-degree regression line is shown.

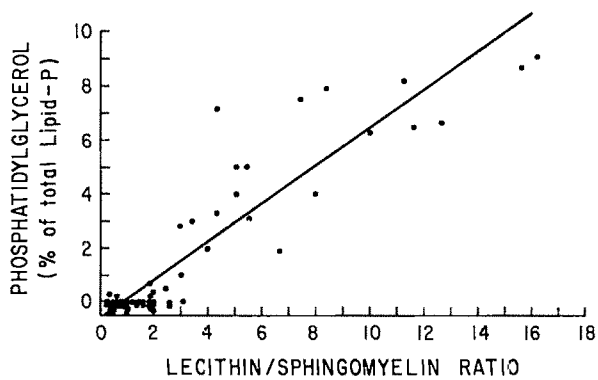


Fig. 2. Relationship between densitometrically determined L/S ratios from acetone-precipitable fractions and PG content assayed by phosphorus *(P)* measurements. Linear regression line is shown ($y = 0.71 x - 0.63$).

stepwise development of these same acidic phospholipids. This and the virtual identity of the unique phospholipid compositions between term amniotic fluid and purified lung surfactant further confirm that the phospholipids in amniotic fluid originate mostly from the fetal lung.

Would the measurement of PI and PG in amniotic fluid be valuable as additional indices of lung maturity?

PG appears when the L/S ratio exceeds 2 (Fig. 2). Substantial quantities of PG indeed indicate lung maturity. However, its absence does not necessarily mean that RDS is inevitable. We have documented cases where PG first appeared within two hours after birth with no symptoms of RDS but with mature L/S ratios. On the other hand, surfactant with prominent PI sometimes was recovered from lung effluent at birth, but PG did not appear and RDS developed. In these cases the L/S ratio was less than 2 or factors

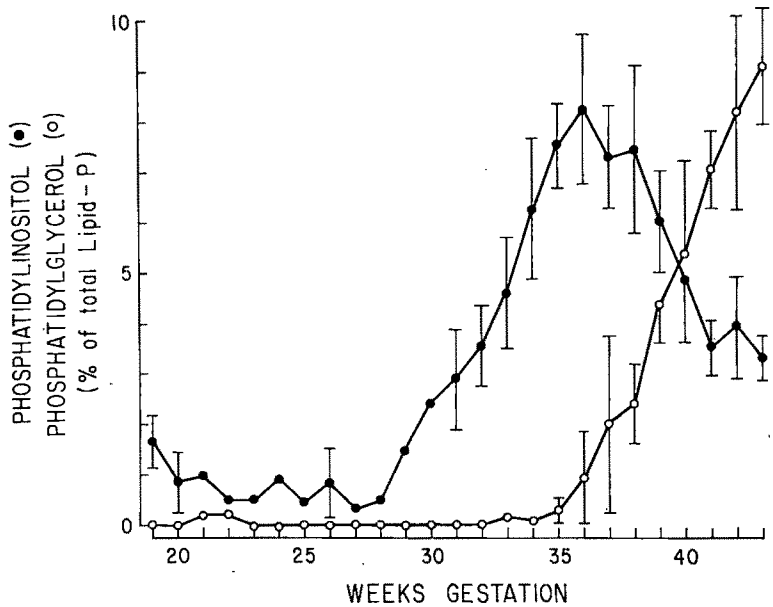


Fig. 3. The content of PI (•) and PG (o) in amniotic fluid during normal gestation. The phospholipids were quantified by measuring the phosphorus *(P)* content and expressed as percentages of total lipid phosphorus. Means ± standard deviations of 3 to 5 samples are shown for each point.

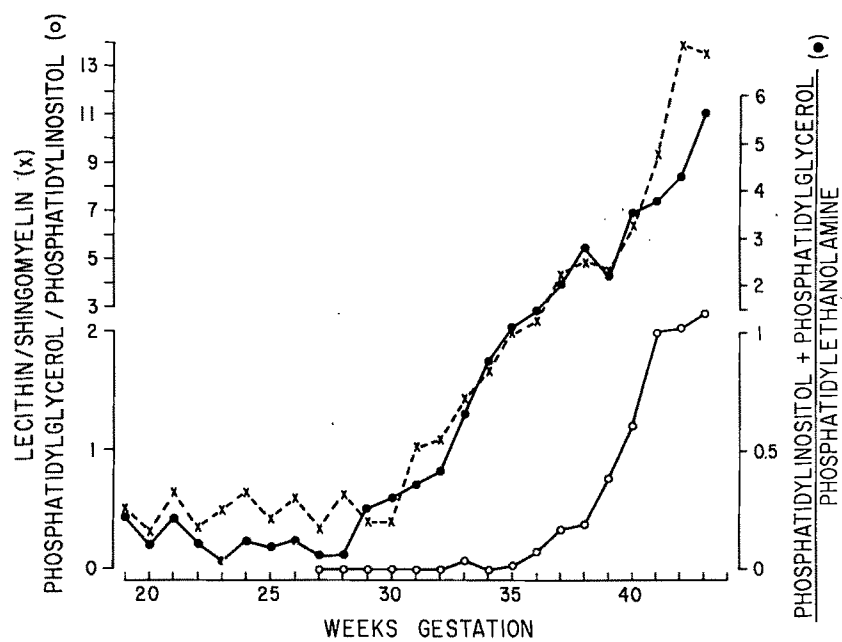


Fig. 4. L/S ratios (X), PG/PI ratios (o), and PI + PG/phosphatidylethanolamine ratios (•) as a function of the gestational age. L/S ratios have been calculated from the acetone-precipitable fraction with reflectance densitometry, and the others were calculated from the total lipid fraction by measuring the phosphorus contents.

depressing phospholipid synthesis, such as hypoxia and acidosis,[7] were present.

Present evidence suggests that PG markedly improves the function of lung surfactant in stabilizing alveoli. Therefore, absent PG in amniotic fluid indicates that the surfactant may not be quite mature. To further define PG as an index of maturity, its function and the factors that regulate and interfere with its development need to be clarified.

The increase in PI closely parallels the L/S ratio up to the value of 2, so that it could be used as an additional index of lung maturity. It and PG also can be recorded with reflectance densitometry, similar to the method used to measure the L/S ratio.

PG and PI are present in very small quantities in blood products whereas lecithin and sphingomyelin found in the blood may interfere with L/S ratio measurements. Blood contamination of the amniotic fluid may prove to be a particular indication to use the acidic phospholipids for evaluation of lung maturity.

The authors acknowledge the help of Dr. Allen Lein in analysis of the statistics.

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Baseline fetal heart rate characteristics as an indicator of fetal status during the antepartum period

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A retrospective study was designed to determine whether the baseline fetal heart rate (FHR), recorded before oxytocin infusion, would have any correlation with the outcome of the oxytocin challenge test (OCT).

THE FETAL monitor, which simultaneously records FHR and uterine activity, has been a recent important advance in obstetric practice. The use of the fetal monitor in labor is well documented.[1, 2]

Increasingly the fetal monitor is also being used in the antepartum evaluation of the high-risk pregnancy. One such method of antepartum use is the OCT, in which oxytocin is used to induce contractions while the fetal heart rate is monitored. These contractions serve as a stress to the fetus and provide some indication of fetal status. Clinical experience with the OCT has been previously described[3, 4] and in our experience continues to be a valuable method for the antepartum evaluation of fetal well-being.

It has been elsewhere suggested that simple monitoring of baseline fetal heart rate without oxytocin stimulation might be sufficient in the antepartum evaluation of some high-risk pregnancies.[5] The OCT is time consuming and is not applicable to patients where oxytocin-induced contractions are contraindicated (placenta previa, multiple gestation, previous classical cesarean section). If one could gain adequate information from the characteristics of the baseline fetal heart rate, as has been suggested,[4] it might be possible to eliminate the need for oxytocin infusion in many patients requiring antepartum fetal evaluation.

This is a retrospective study designed to see if the baseline FHR, recorded before oxytocin infusion, would have any correlation with the outcome of the OCT.

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Methods

1. Patient selection. From January, 1970, to July, 1973, 703 OCT's were carried out on 337 patients. Of these tests, 457 were performed with phonocardiography and 246 were performed with ultrasonic sensors for FHR recording. Because of the difficulty in evaluating baseline variability in those tests done with ultrasound, only those tests done phonocardiographically were examined (see No. 2 method of evaluation). To be included in this study the OCT recording must have demonstrated the following: (a) an adequate baseline of 5 or more minutes before oxytocin infusion was begun, (b) a technically good quality recording with data from both the uterine contraction and FHR channels, and (c) an eventual reading as either a positive, a negative, or suspicious OCT (see No. 4 below for interpretation of OCT).

Of the 457 OCT's examined, 255 were eligible for the study by the above criteria. The rest were eliminated because an adequate baseline was not obtained prior to oxytocin infusion (147 tests) or because the OCT was read as unsatisfactory for interpretation (47 tests) or hysterstimulation (eight tests). Such a large number were eliminated because at the time the tests were performed, the individuals doing the tests were not specifically interested in preoxytocin baseline information and often did not obtain a baseline of adequate length prior to beginning the oxytocin infusion.

2. Method of evaluation. Evaluation of FHR characteristics prior to oxytocin infusion was done without the

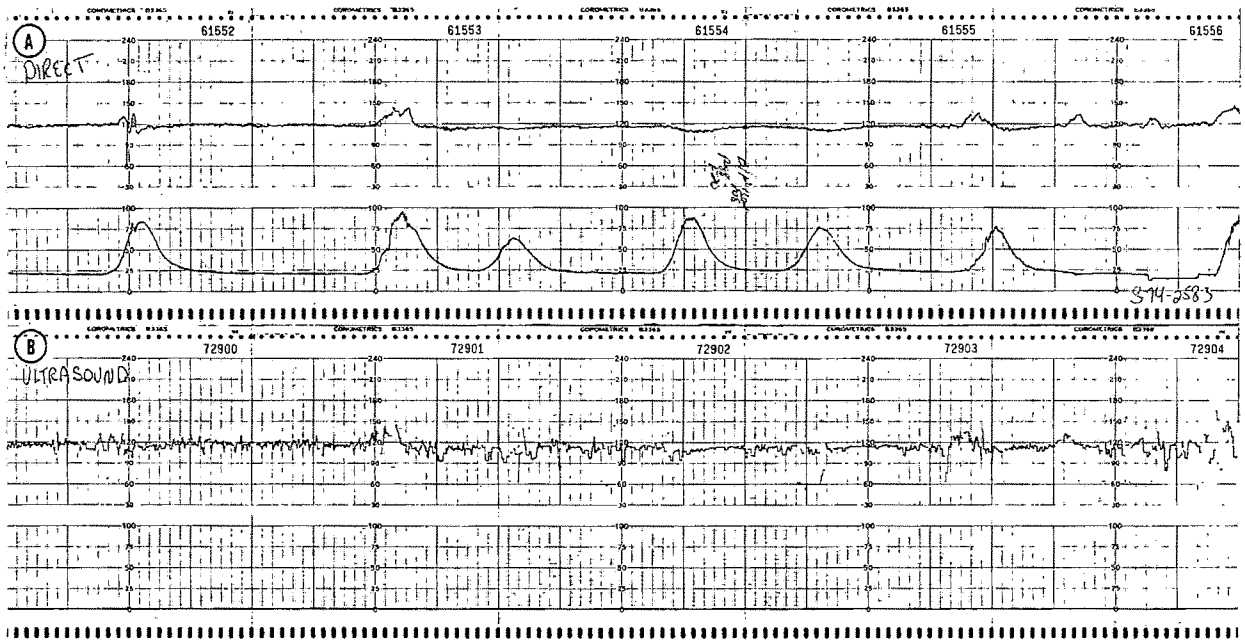


Fig. 1. Comparison of simultaneous recordings using direct FECG (Panel *A*) and ultrasound techniques (Panel *B*). Note the false impression of increased FHR variability introduced by the ultrasonic monitor.

evaluator's knowledge of the subsequent outcome of the OCT. The two features studied were baseline variability and acceleration of the FHR with fetal movement.

A. Baseline variability. Baseline variability was difficult to assess for the following reasons.

1. The true variability of the FHR derived from fetal electrocardiographic (FECG) signals cannot be reliably reproduced with external ultrasonic or phonocardiographic monitors. This is because the character of the basic signal is much less precise, and the electronic logic necessary for adequate function of external monitors often introduces artifact. We have found that external FHR monitoring with a phonocardiographic system* has less increased variability artifact than ultrasound.† It is for this reason that only phonocardiographic tracings were used in this study (Figs. 1 and 2). Even with phonocardiography, however, one cannot be assured that true baseline FHR variability is being measured.

2. The basic FHR variability characteristics appear to change from time to time in a given fetus, making the time of sampling critical (see Fig. 3). The magnitude of the baseline variability was calculated by measuring the "peak to valley" difference in the long-term (3 to 6 cycle per minute) oscillations during a 2 minute interval when there were no periodic FHR changes related to uterine contractions or fetal movement. In preliminary observations it appeared that a variability of 20 beats per minute or greater was an appropriate cutoff when correlating with negative OCT results. It should be noted that there is a degree of subjectivity inserted when picking an appropriate area to measure variability and for this reason it was felt to be important, for this study, that the evaluator not know the subsequent results of the OCT or anything about the patient being studied. The records were, therefore, prepared by a second party prior to evaluation so no patient information or OCT outcome results were available to the evaluator.

B. Acceleration of the FHR with fetal movement. Because of the observation that acceleration of the FHR at the time of fetal movement seemed to occur in fetuses that had negative OCT results, this finding was also noted during the baseline monitoring period prior to oxytocin infusion. The accelerations counted had to exceed 20 beats per minute above the baseline FHR and were associated with sharp spike excursions on the UC channel presumably due to fetal movement (see Fig. 4).

*Modified Corometrics FMS 101A with Toiutsu microphone and manual gain control Corometrics Medical Systems, Wallingford, Connecticut.

†Standard Corometrics FMS 101B, Corometrics Medical Systems, Wallingford, Connecticut.

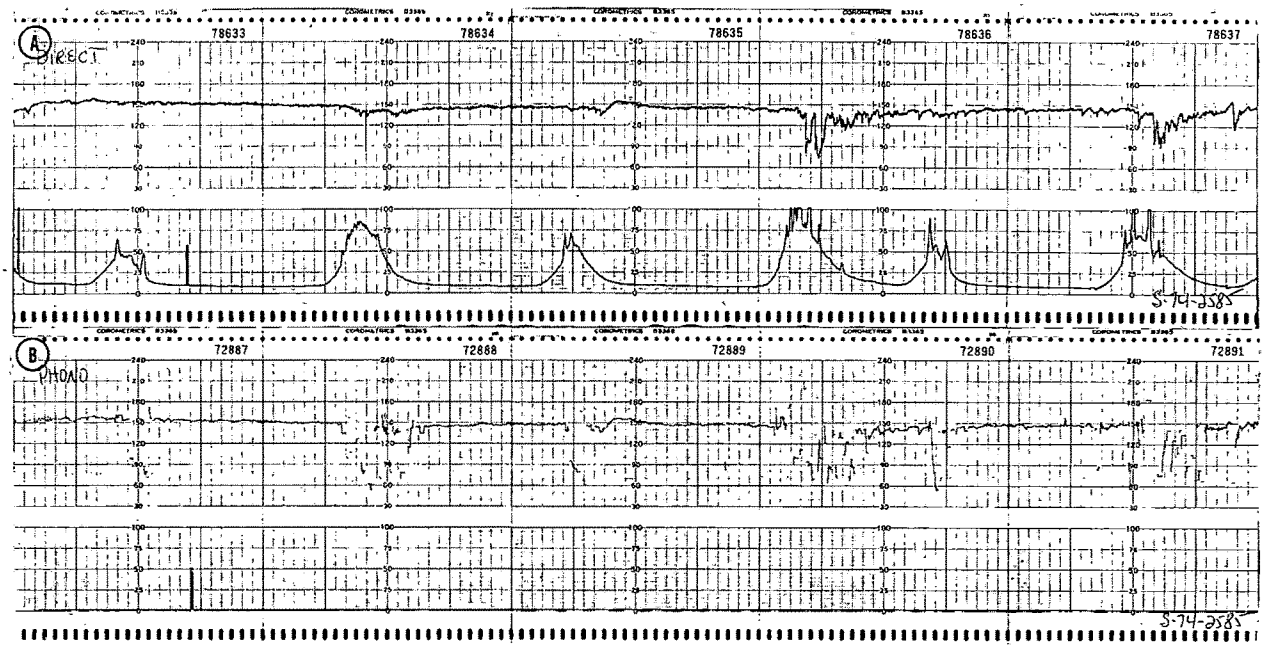


Fig. 2. Comparison of simultaneous recordings using direct FECG (Panel *A*) and phonocardiographic techniques (Panel *B*). Note the variability of the baseline FHR appears similar but there is some signal loss during contractions with phonocardiography.

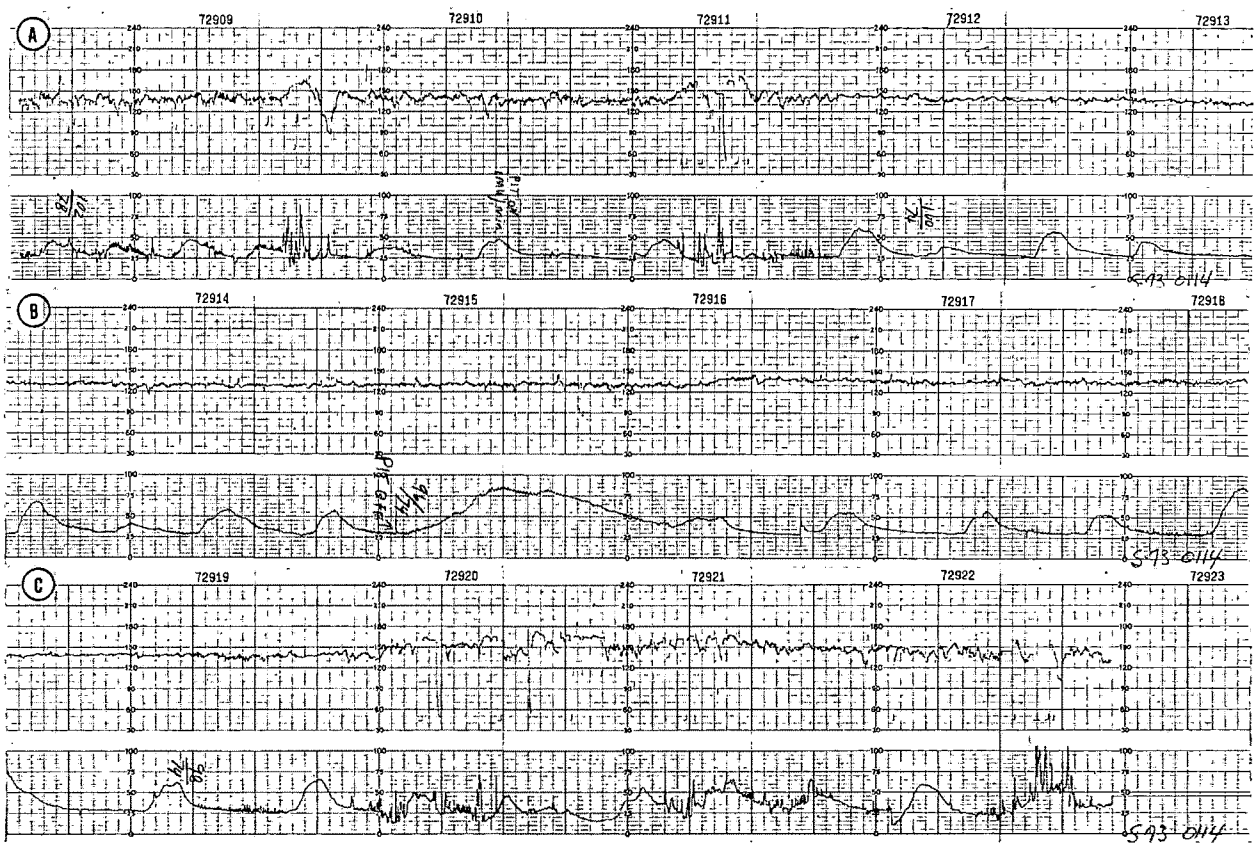


Fig. 3. An example of a marked change in baseline variability at different times in the same patient.

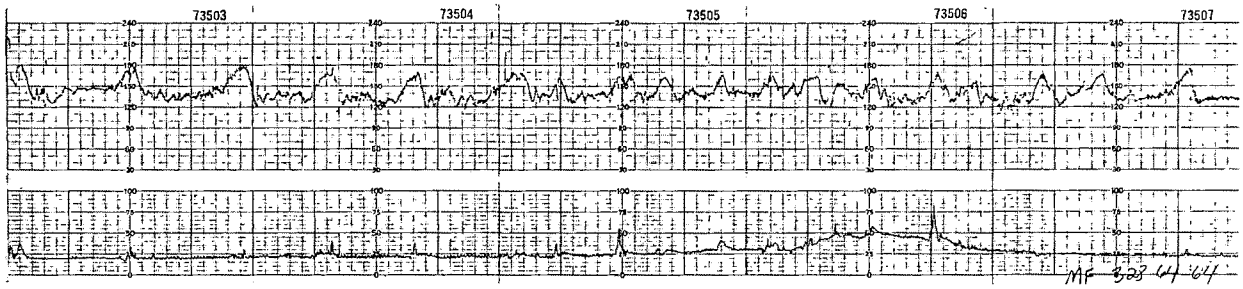


Fig. 4. An example of acceleration in fetal heart rate that accompanies fetal movement. Note that the sharp spikes on the uterine contracton channel, which indicate fetal movement, are associate with concomitant FHR accelerations.

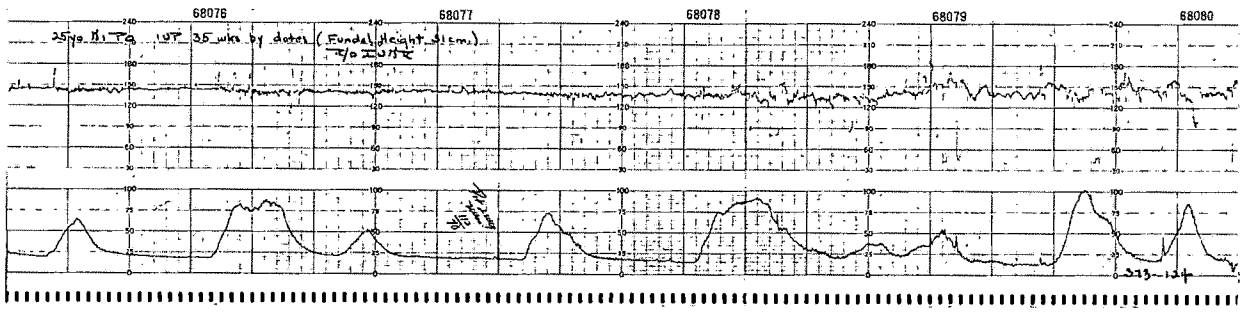


Fig. 5. An example of a negative oxytocin challenge test.

These records were then evaluated as to whether FHR acceleration with fetal movement as described was present or absent.

3. Procedure for the OCT. The patients were placed in the semi-Fowler position and an external fetal monitor* was attached. Baseline fetal heart rate and uterine activity were recorded. Blood pressure was taken every 10 minutes throughout the test. Infusion of oxytocin was begun with a Harvard† constant infusion rate pump at 0.5 to 1.0 milliunit per minute. The rate of infusion was doubled every 10 to 20 minutes until a uterine contraction frequency of at least three contractions per 10 minutes was obtained. After an adequate contraction frequency was obtained, the oxytocin infusion was stopped and the patients were observed for 10 to 15 minutes or until the uterine activity returned to its baseline value. An adequate test usually requires 1½ to 2 hours to complete and is performed by a registered nurse or physician.

4. Interpretation of the OCT. The OCT is read as follows: (a) *Negative:* uterine contractions occurring at a rate of at least three per 10 minutes and no late decelerations in the fetal heart rate (Fig. 5); (b) *Positive:* consistent late decelerations occurring with most uterine contractions in the absence of hyperstimulation (Fig. 6) (hyperstimulation is defined as contractions occurring more often than every 2 minutes or lasting more than 90 seconds); (c) *Suspicious:* intermittent late decelerations occurring inconsistently and not associated with hyperstimulation (Fig. 7).

If spontaneous contractions are occurring at a frequency of three per 10 minutes this is considered an adequate test. If consistent late decelerations occur with a spontaneous contraction frequency of less than three per 10 minutes the test is called positive and it is not necessary to increase uterine activity with oxytocin.

*Corometrics FMS 101A with modified acoustical Toiutsu transducers, Corometrics Medical Systems, Inc., Wallingford, Connecticut.

†Harvard Apparatus, 150 Dover Rd., Millis, Massachusetts 02054.

Results

Baseline FHR variability during the preoxytocin infusion period exceeded 20 b.p.m. in 77 of the 255 tests studied. Acceleration of the FHR temporally related to fetal movement was noted in 75 of the 255 tests. There was only one patient who subsequently had a positive OCT when baseline variability was greater than 20 b.p.m. When accelerations with fetal movement were noted during the preoxytocin baseline

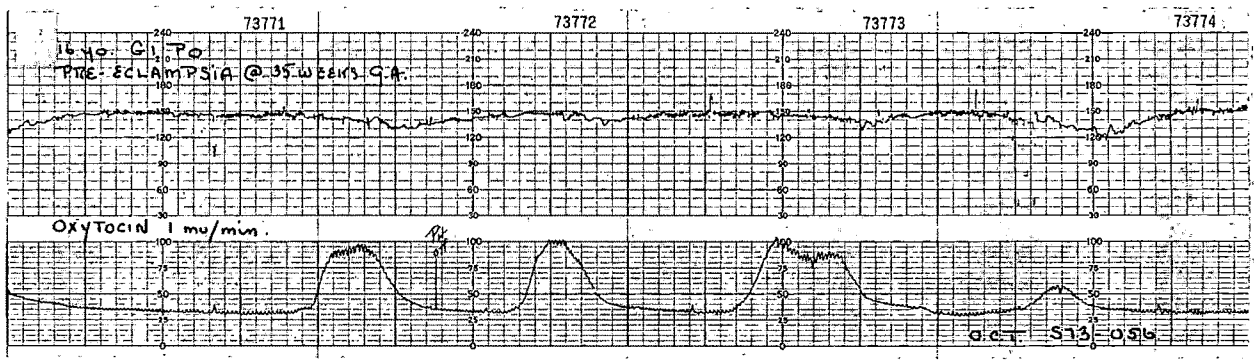


Fig. 6. An example of a positive oxytocin challenge test.

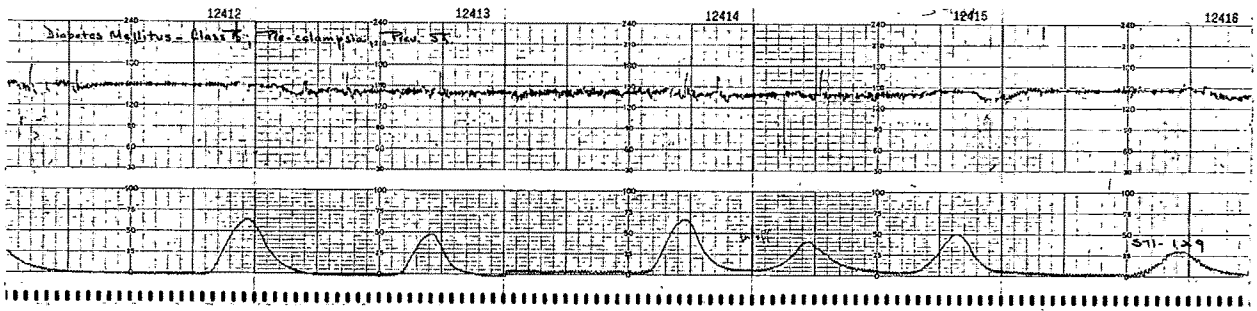


Fig. 7. An example of a suspicious oxytocin challenge test.

Table I. Antepartum fetal monitoring, two baseline variables (255 OCT's)

Variability	*Acceleration with fetal movement*	*No.*	*Neg.*		*Post.*		*Susp.*	
			No.	*%*	*No.*	*%*	*No.*	*%*
>20 b.p.m.	(+)	41	40	98	0	0	1	2
>20 b.p.m.	(−)	36	32	89	1	3	3	8
<20 b.p.m.	(+)	34	29	85	0	0	5	15
<20 b.p.m.	(−)	144	110	76	24	17	10	7

recording, no patient had a positive OCT during subsequent oxytocin administration.

There were 178 tests that showed a baseline variability less than 20 b.p.m. In this group 24 of 178 (14 per cent) had a positive OCT during the oxytocin infusion period. There were 180 tests that showed no acceleration of the FHR with fetal movement prior to oxytocin infusion. In this group 25 of 180 (14 per cent) had a positive OCT during the oxytocin infusion period.

In those tests in which there was both no acceleration with fetal movement and variability less than 20 b.p.m. in the baseline FHR, 24 of 144 tests (17 per cent) showed a subsequent positive OCT during oxytocin administration (see Tables I and II). It should be noted that there were a significant number (8 per cent) of suspicious test results which showed acceleration with fetal movement during the preoxytocin baseline period. None of these patients had a subsequent positive test.

Comment

Variability of the FHR appears to be characteristic of fetal well-being.[6–8] A "reactive" fetus has been characterized by one whose FHR accelerates in response to external stimuli or during fetal movement.[9] As we have gained more experience with the heart rate characteristics of the fetus during the antepartum period it became apparent that some fetuses were quite reactive (and sometimes difficult to monitor because of their activity) while others were characterized by very little movement with associated FHR acceleration (non reactive) and they also often showed decreased baseline FHR variability.

Further observations suggested that the "reactive"

fetus was virtually always in apparent good condition. On the contrary, it appeared that a fetus who had minimal variability of the baseline FHR and no acceleration of the FHR with fetal movement during the baseline recording period (a nonreactive fetus) was more likely to have a positive OCT. This retrospective study was carried out to see how close, if any, the correlation would be between FHR variability and acceleration of the FHR with fetal movement and subsequent results of an OCT.

The data in this study reveal that acceleration of the FHR with fetal movement, when present during a 5 minute baseline recording period, was not associated with late deceleration during a subsequent OCT. Only one patient had a positive OCT who demonstrated FHR variability over 20 b.p.m. during the baseline period. Baseline FHR variability is difficult, however, to evaluate with currently available external monitors. Acceleration of the FHR with fetal movement is an easily identifiable endpoint and would, therefore, appear to be the more valuable of the two parameters for evaluating fetal well-being by nonstressed technique. Caution must be exercised in interpreting the clinical value of acceleration of the FHR with fetal movement until studies are carried out which demonstrate the validity of this observation when used for prospective patient managenent. If such studies reveal that FHR acceleration with fetal movement is indeed a reliable sign of fetal well-being, the logistics of such nonstressed antepartum FHR testing would be considerably simpler reducing the time for a test from 2 hours to 10 minutes.

Table II. Antepartum fetal monitoring, single baseline variable (255 OCT's)

		Neg.		*Pos.*		*Susp.*	
	No.	*No.*	*%*	*No.*	*%*	*No.*	*%*
Variability > 20 b.p.m.	77	72	94	1	1	4	5
Variability ≤ 20 b.p.m.	178	139	78	24	14	15	8
Acceleration with fetal movement	75	69	92	0	0	6	8
No acceleration with fetal movement	180	142	79	25	14	13	7

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Uterine blood flow, oxygen consumption, and maternal plasma estradiol and progestins following fetal death

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Fetuses of 42 near-term sheep were killed while they were in utero. Uterine blood flow, oxygen consumption, A-V O_2, and maternal arterial plasma concentrations of estradiol and progestins were observed for the next 4 hours. There was an immediate (88 per cent) fall in oxygen consumption; blood flow decreased by 50 per cent within 30 minutes. Hormone concentrations changed, but only after 2 hours. Circulatory changes appeared to be related to local changes within the uterus, particularly to decomposition of the chorioallantoic membrane. This relationship was best seen in the experiments in which one of a set of twins was killed. The experiments are in accord with the theory that the rate of uterine blood flow is not directly related to acute changes in respiratory gases nor to plasma concentrations of certain hormones.

DURING THE last half of gestation in sheep, the rate of blood flow to the uterus expressed in milliliters per kilogram per minute tends to be constant as total flow (in milliliters per minute) appears to increase in direct proportion to increments in the combined weight of fetal, placental, and uterine tissues.[1] Of the mechanisms thought to establish and maintain this relationship, two have received most serious consideration: the mean oxygen pressure within the uterine circulation and the hormones estrogen and progesterone.

Studies in which blood was sampled by chronically implanted catheters suggest that oxygen may regulate the uterine vascular bed during pregnancy. In sheep and goats,[2] horses,[3] and pigs (Caton: Unpublished data), uterine venous Po_2 and uterine arteriovenous oxygen difference (A-V O_2) tend to be constant throughout the last half of gestation—the time when growth is greatest and total requirements for oxygen of the uterus and its contents increase most rapidly. Further evidence has come from studies of sheep bred and kept at high altitude.[4] At all stages of pregnancy their rates of uterine blood flow tend to be higher than those of sheep kept at sea level.

The mechanisms which may relate uterine blood flow and oxygen are unknown. Acute hyper- and hypoxemia appear to have little effect on flow rate[5] and ischemia of the uterus is not followed by a period of reactive hyperemia.[6] Similarly, the oxygen saturation of uterine venous blood rises abruptly at death of the fetus[7] or when the cord is clamped at cesarean section (H. Prystowsky: Personal communication) and it may persist for some time. These observations suggest that sudden changes of oxygen partial pressure or content within the uterine vasculature do not induce an immediate, commensurate change in blood flow. They do not exclude the possibilities that the response of uterine vascular bed to oxygen may be slow; that oxygen may exert its effect directly, by stimulating

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vessel growth, or indirectly, by altering the rate of metabolism of some other substance which in turn effects blood vessel tone or growth.

The relationship between estrogens, progestins, and vascular changes within the uterus has been recognized since the early part of the century from studies relating ovarian structure and function to various phenomena of estrous and menstrual cycles. They appear to affect both vessel growth and tone. Markee[8] documented the former in his classic studies of endometrium transplanted into the anterior chamber of the eye of the monkey. His observations have been supported by studies of other species.[9, 10]

Markee also observed arteriolar constriction and dilatation that appeared to cause changes in the rate of perfusion of the endometrial grafts. These were hormonally induced and were related to the administration of estrogens and progestins alone or in various combinations. Presumably, similar changes in vascular resistance account for variations in uterine blood flow observed in intact, nonpregnant sheep during the estrous cycle. Greiss and Anderson[11] and Huckabee and associates[12] observed highest rates during behavioral estrous or when the ovary contained a follicle and observed lowest rates when the ovary contained one or more well-developed corpora lutea. These changes were independent of the mean oxygen pressure within the uterine circulation. That is to say, the rate of oxygen consumption of the uterus tended to be constant so that the rate of blood flow and A-V O_2 across the uterus were inversely related. On the other hand, all conditions characteristic of the follicular stage of the cycle could be mimicked by administering various estrogen compounds.[6, 13] Moreover, progesterones administered concurrently appear to inhibit or antagonize the effect of estrogens so that the rate of blood flow and A-V O_2 reflect the ratio between amounts of the different hormones.[14]

It has been suggested that estrogens and progesterone also may regulate uterine blood flow during pregnancy. Although the rate of blood flow (in milliliters per kilogram per minute) and uterine A-V O_2 tend to be constant during the latter half of gestation, they differ from values measured in the first 60 days.[15] The transition which may take place within a few days[16] occurs at the earliest time the ovaries may be removed without termination of the pregnancy[17] and when peripheral plasma concentrations of progesterone start to rise.[18] The inference which attributes the fall in rate of blood flow to increased amounts of progesterone released by the chorioallantoic membrane is supported by the observation that large dosages of progesterone given to ewes prior to day 60 of pregnancy are associated with a similar decrease in rate of blood flow.[19]

We undertook these experiments to learn more of the mechanisms which regulate the rate of blood flow to the pregnant uterus, particularly its relationship to oxygen and plasma hormones. The fetuses of near-term sheep were killed while they were in utero, thereby causing an abrupt change in the oxygen metabolism of the uterus and its contents as well as a rise in the mean oxygen pressure of blood in its circulation. Subsequent changes in blood flow were observed, in particular, the way in which the rate changed in relation to uterine A-V O_2 content and to concentrations of estradiol and progestins in arterial plasma. We hoped in this way to gain insight as to the role of these factors in the regulation of uterine blood flow in normal circumstances.

Materials and methods

Studies were carried out on 42 mixed-breed sheep supplied to us by the Department of Animal Science. All appeared to be in good health, had known breeding dates, and were within 2 weeks of term (146 days).

Food, but not water, was withheld for 2 days prior to the experiment. Ewes were anesthetized with oxygen and methoxyflurane (Metafane, Pitman-Moore) and their abdomens opened with a midline incision long enough to deliver the tips of both uterine horns into the wound. Fetal membranes were exposed through a small incision in the uterine wall and polyvinyl catheters (0.034 and 0.022 inches external and internal diameters, respectively) were threaded into a small vein and artery until their tips came to lie in the umbilical cord near the body wall of the fetus. Maternal catheters were placed in each main uterine vein and into the aorta and inferior vena cava via appropriate femoral vessels. All catheters were brought out through a stab wound in the flank.[2] Wounds were closed and the animals allowed to recover from anesthesia. In no instance did surgery exceed 60 minutes. Experiments were performed the same day, but only after the animals had awakened and were standing.

In the first group of experiments, fetuses of 13 ewes were killed by injecting either a bolus of air (50 ml.) or a saturated solution of KCl (10 ml.) through the umbilical vein catheter. (Both injectates stopped umbilical arterial pulsations equally fast and there was no difference in subsequent observations related to which had been used.) Blood flow to the uterus was measured starting either 20, 110, or 230 minutes thereafter. Four other ewes were studied while the fetus was alive.

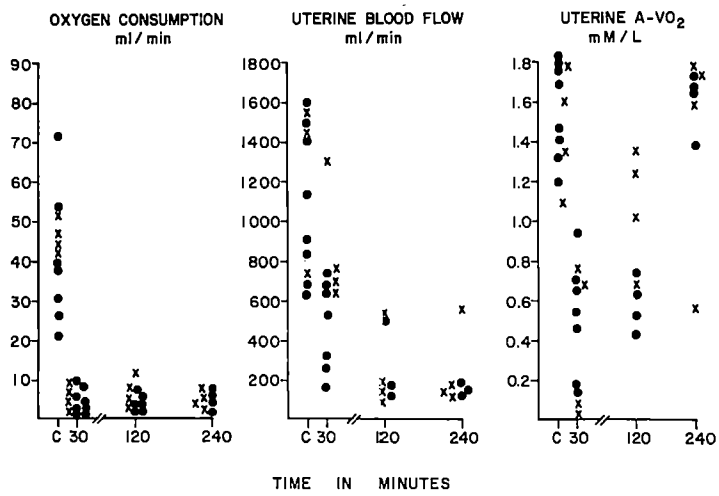


Fig. 1. Changes in total oxygen consumption and uterine blood flow (milliliters per minute) and A-V O_2 of sheep before and after death of the fetus. × indicates single observations in which flow was estimated by the Fick method. Dots are from studies in which two or more estimates were made on the same animal with the scheme described in the appendix.

In the first group of sheep, rate of uterine blood flow (milliliters per minute) was estimated by the Fick principle in accord with methods already described,[20] with the use of antipyrine as the marker substance. At the end of the flow test period, the animal was quickly reanesthetized with an intravenous bolus of pentobarbital. The broad ligament and cervix were clamped and the uterus was excised intact. Amniotic and allantoic fluids, the fetus, cotelydons and membranes, and uterus were examined and weighed separately. Aliquots of each were extracted for antipyrine.[21]

Arterial and uterine vein blood samples, collected in the course of the blood flow estimation, were analyzed for their oxygen content with a manometric Van Slyke apparatus and for P_{O_2}, P_{CO_2}, and pH with standard electrodes at 38° C. and an Instrumentation Laboratories apparatus Model S-2. The remaining blood was centrifuged. Arterial plasma was separated and stored at −15° C. until concentrations of antipyrine and of estradiol and progesterone could be measured as described below.

To enable us to make more than one set of observations on the same animal we developed another scheme to estimate total uterine blood flow (milliliter per minute) before and at selected intervals after fetal death. With it, we studied a second group of 25 sheep. They were prepared as described above. An estimation of the blood flow to the uterus was made while the fetus was alive with a diffusion equilibrium method which estimates the rate in milliliters per kilogram per minute. The fetus was killed and one or more repeat determinations were made during the next 4 hours. After the last observation each animal was reanesthetized, her uterus was excised, and the tissues were examined and analyzed for their antipyrine content. Total blood flow (in milliliters per minute) after fetal death was calculated according to methods described in the Appendix.

From studies of animals of the two groups, data were available to calculate the rate of uterine blood flow by the diffusion equilibrium method. This method substitutes the concentrations (in milligrams per 100 ml.) of antipyrine in uterine venous blood 20 minutes after the start of the infusion for the total amount of antipyrine (in milligrams) in the numerator of the Fick equation. In this case, flow rate is expressed as milliliters per kilogram of perfused tissue per minute. This method is applicable in circumstances in which all tissues nourished by uterine blood are in antipyrine equilibrium with uterine-venous blood. This condition is satisfied when the fetus is alive (Appendix); therefore, the calculation was made only in such circumstances. All antipyrine concentrations were measured according to the method described by Meschia.[22] To calculate oxygen consumption (milliliters per minute or milliliters per kilogram per minute) of tissue nourished, the arteriovenous oxygen difference was multiplied by each measurement of the rate of uterine blood flow expressed in milliliters per minute or milliliters per kilogram per minute.

Eight ewes carried twins and umbilical catheters were placed in each. The placenta of each twin tends to be confined wholly to one or the other horn and there is little mixing of maternal venous blood from the

Table I. Antipyrine equilibration between uterine venous blood and various tissues and fluids

Sheep	*Antipyrine in uterine venous blood 20 min. after start of infusion (mg./100 ml.)*	*Antipyrine concentration expressed as a per cent of concentration in uterine venous blood*				
		Fetus	*Uterus*	*Placenta**	*Amniotic*	*Allantoic*
Alive:						
R53	3.10	94	64	67	40	22
B30	4.05	95	81	78	32	18
B16	3.73	99	84	72	20	12
W74	4.79	101	—	—	25	17
Mean		97	76	72	30	17
20 min.:						
240	6.29	0	81	60	38	16
N.T.	5.46	0	112	75	18	9
Y238	6.49	0	90	54	16	7
Y236	5.67	0	93	77	14	15
Mean		0	94	67	22	12
110 min.:						
Y37	4.91	0	105	57	16	14
B14†	4.48	0	85	37	36	12
B14†	—	0	—	—	33	13
W67	5.85	0	48	22	25	5
Y229	3.52	0	39	16	11	4
W28	5.10	0	41	22	16	17
Mean		0	64	31	25	11
230 min.:						
Y36	4.96	0	48	22	15	16
Y61	4.64	0	48	24	16	7
Y59	5.63	0	53	32	‡	‡
Y246	5.78	0	46	31	16	8
Mean		0	49	27	15	11

*Placenta refers to membranes and cotelydons.

†Twins.

‡Antipyrine equilibration in amnionic and allantoic fluids combined was 11 per cent.

two sides.[23] Therefore, each horn of the uterus was treated as a separate organ. Blood was collected simultaneously from both main veins during and after antipyrine infusion. Each fetus, its placenta, and those portions of the uterus contiguous with it were weighed separately. Appropriate analyses for antipyrine and oxygen were carried out so as to allow us to estimate the blood flow, oxygen consumption and A-V O_2 to each horn of the uterus. In most experiments estimates were made before and after death of one or of both twins using the scheme to measure blood flow outlined in the appendix. In two experiments flow was measured by the Fick method only after death of the fetus.

Plasma progestins were measured by radioimmunoassay of iso-octane extracts. Final quantification was adjusted for procedural losses by recovery of progesterone-1,2^3-H (3,000 d.p.m.) which was added to the pre-extracted plasma (0.5 ml.). A radioimmunoassay procedure, as described by Abraham and associates,[24] was developed for progesterone and validated in our laboratory.[25]

Plasma estradiol was extracted with diethyl ether (three volumes) and isolated from estrone by Sephadex LH-20 column chromatography (benzene:methanol 90:10; 5 Gm. of presoaked Sephadex LH-20 poured into a 2.5 ml. glass syringe). Isolated estradiol was measured with a radioimmunoassay technique comparable to that described by Hotchkiss and associates.[26] Final estradiol measurements were corrected for procedural losses with estradiol 17β-2,4,6,7^3-H added to 5 ml. of the pre-extracted plasmas. The quantification system for plasma estradiol also has been described and validated in our laboratory.[25]

Results

Fetal death was followed by marked changes in the appearance of the reproductive tract. Within 2 hours uterine arteries and veins (those of the myometrium as well as of the broad ligament) appeared to be smaller in diameter and the irritability and contractility of the myometrium increased. The membranes first lost their transparency, became translucent, and then opaque. By 4 hours they were brown and friable at their junction with the cotyledons so that maternal and fetal tissues separated easily. By that time the cotelydons

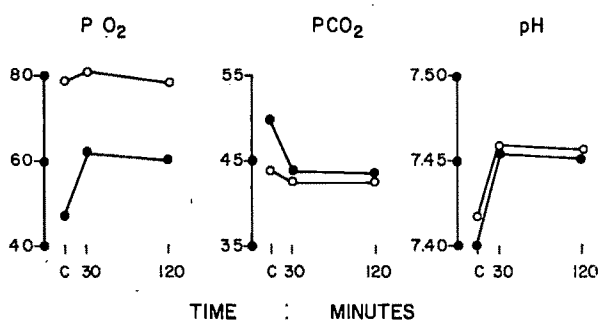


Fig. 2. Changes in arterial (open circles) and uterine vein (closed circles) po_2, pco_2, and pH of one typical animal. Data are given before *(C)* and 30 and 120 minutes after fetal death.

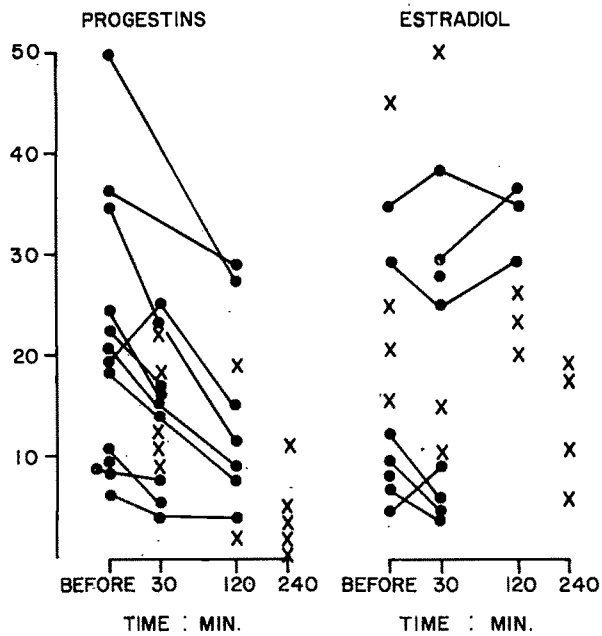


Fig. 3. Arterial plasma concentrations of estradiol (picograms per milliliter) and progestins (nanograms per milliliter). Lines connect repeat determinations on the same sheep; ×, one observation only.

were round rather than flat and pinched around their base so that they appeared to be suspended from the mucosa by a pedicle. The uterine mucosa appeared to become more pale with time and it and the myometrium bled less when cut.

Concentrations of antipyrine in various tissues and fluids (expressed as a percentage of the concentration in uterine venous blood 20 minutes after the start of the antipyrine infusion) are given in Table I. When the fetus was alive equilibration was virtually complete. In those experiments in which the fetus was dead at the time of the infusion, no antipyrine was found in its tissue. Equilibration of antipyrine between uterine venous blood and the myometrium and between uterine venous blood and the placenta was less complete, and smaller concentrations were measured in amniotic and allantoic fluids.

Rates of total blood flow to the uterus, estimated with the scheme described in the appendix, appeared to be substantially the the same as those measured by the direct Fick method (Fig. 1). For brevity, these data have been combined. When the fetus was alive total blood flow to the uterus averaged 1,136 ± 36 ml. per minute (S.E.M., n = 12). Thirty minutes after fetal death it was 611 ± 95 ml. per minute (n = 11). At 2 and 4 hours, respectively, it was 243 ± 63 (n = 7) and 155 ± 25 n = 7) ml. per minute.

The A-V oxygen difference fell from a mean of 1.73 ± 0.19 (S.E.M.) mM. per liter when the fetus was alive to 0.47 ± 0.09 mM. per liter 30 minutes after death—a decrease which averaged 73 per cent. At 2 hours the mean value had increased to 0.86 ± 0.11 mM. per liter and by 4 hours it was 1.55 ± 0.18 (Fig. 1). Measurements of arterial Po_2, pco_2, and pH tended to be constant but there were systematic changes in the uterine vein consistent with the changes in A-V O_2 content. Data for one typical animal are shown in Fig. 2.

Fetal death was followed by an abrupt change in the total oxygen consumption of the uterus and its contents (Fig. 1). Values ranged from 20 to 72 ml. per minute (40.4 ± 1.3 mean and S.E.M.) during the control period. Thirty minutes after fetal death the mean value was 4.6 ± 0.8, an average decrease of 88 per cent. There was little further change between the second and fourth hours; 5.1 ± 0.6 and 4.9 ± 0.7 ml. per minute, respectively.

Rates of uterine blood flow measured by diffusion equilibrium method on sheep with a live fetus averaged 247 ± 14 (S.E.M, n = 14) ml. per kilogram per minute. Rates of uterine oxygen consumption calculated from these data averaged 8.47 ± 0.71 (S.E.M.) ml. per kilogram per minute.

Maternal arterial plasma estradiol concentrations averaged 19.5 ± 4.0 pg. per milliliter when the fetus was alive. Values at 30 minutes and at 2 and 4 hours after fetal death averaged 20.2 ± 4.1, 26.3 ± 2.4, and 16.7 ± 3.6 pg. per milliliter, respectively (Fig. 3).

In the eight ewes which carried twins, there appeared to be no significant difference between values of A-V O_2, rates of blood flow, and oxygen consumption of the two uterine horns when both fetuses were alive or when both were dead. However, in those experiments in which observations were made after killing one twin, bilateral differences were observed. Changes from control tended to occur only in the horn containing the dead fetus (Table II). Differences in the appearance of the two horns of the uterus and of the

membranes were distinct so that within an hour we could identify which contained the dead fetus by inspecting the intact uterus in situ.

Comment

Our observations on sheep with a live fetus are in agreement with data already in the literature. Rates of uterine blood flow, oxygen consumption, and A-V O_2 are similar to those obtained in acute and in chronic studies by Huckabee and associates.[15, 16] Values of plasma progestins are comparable to those measured by Bassett and associates.[18]

In the experiments reported here, fetal death was followed by an abrupt decrease in the total amount of oxygen consumed by the uterus and its contents. Total uterine blood flow also decreased but the initial change proportionately was not as great, which accounts for the uterine A-V O_2 narrowing.

The tendency for the blood flow to remain high despite the decrease in oxygen consumption of the uterus and its contents may explain an observation by Clapp and associates.[27] When they clamped the umbilical cord of the fetus in utero they observed that the oxygen saturation of mixed venous blood increased. This would be expected if uterine blood flow and cardiac output were unchanged even though the oxygen consumption of the uterus and its contents fell as a consequence of umbilical cord clamping. Presumably, the same changes account for Prystowsky's (personal communication) observation in human subjects that uterine venous blood brightens and the oxygen saturation appears to increase when the umbilical cord is clamped during cesarean section.

The original proportion between rates of uterine blood flow (milliliters per minute) and oxygen consumption (milliliters per minute) was re-established between the second and fourth hours after fetal death. That is to say, the A-V O_2 content of most animals rose to its original value. Presumably, this was a consequence of a further decrease in uterine blood flow rather than a change in oxygen consumption. At that time, the flow rate was lowest, the arteries in the broad ligament and those beneath the serosal surface of the uterus were more constricted, and the uterine mucosa was pale.

Values of uterine A-V oxygen content before and immediately after fetal death are in good agreement with those of Raye and associates.[7] They mention no measurements beyond that time which might be useful for further comparison. Changes in the rate of uterine blood flow (milliliters per minute) after fetal death were different because they observed little or no decrease in the first few hours and a decrease of only 30 per cent after one day.

The tendency for a smaller fraction of uterus and

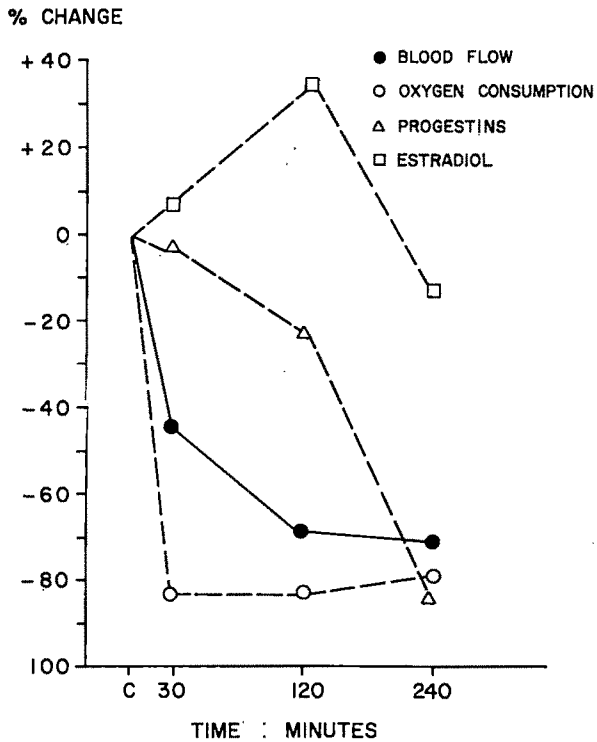


Fig. 4. Changes in uterine blood flow, oxygen consumption, progestins, and estradiol concentration in relation to death of the fetus. The mean values were calculated for each time and expressed as a percentage change from measurements made during the "control" *(C)* period.

placenta to achieve equilibrium with antipyrine of uterine venous blood after fetal death (Table I) may be related to several factors: (1) increased intracapillary distance, (2) decreased tissue perfusion per unit time, or (3) large areas of tissue not perfused at all. In view of findings discussed above, all explanations are likely. If amniotic and allantoic fluids had contained no antipyrine, it would not have been surprising, as fetal circulation had stopped long before antipyrine was infused into the mother. As it was, small amounts did accumulate, despite decomposition of fetal membranes.[1] Presumably, the antipyrine moved from the uterine mucosa across the chorioallantoic membrane by diffusion. If so, it raises interesting questions concerning mechanisms which determine the composition of amniotic and allantoic fluids in normal circumstances.

Data from experiments in which only the Fick method was used to measure uterine blood flow stand by themselves. Material from the second group of sheep, studied with methods outlined in the Appendix, are supplementary. Despite the difference in methodology they are in agreement.

In view of the evidence which suggests that estrogens

Table II. Comparison of twin pregnancies—one or both sacrificed

Ewe	*Uterine blood flow* (ml./min.)*			*A-V O_2 (mM./L.)*		
	Before sacrifice	*20 min. after sacrifice*	*A later time (hr.)*	*Before sacrifice*	*20 min. after sacrifice*	*A later time (hr.)*
Both twins sacrificed (E):						
213yE	309	67	60 (1)	1.99	0.70	0.70 (1)
E	463	38	77 (1)	1.99	0.70	0.70 (1)
52E	687	42	58 (1)	3.01	0.23	0.27 (1)
E	827	55	29 (1)	3.14	0.25	0.23 (1)
227E	309	112	67 (2)	3.11	0.62	1.80 (2)
E	463	169	71 (2)	2.16	0.96	1.99 (2)
15wE	742	299	—	1.31	0.57	0.65 (3)
E	693	298	—	1.04	0.58	0.65 (3)
B14* E	—	—	33 (2)	—	—	1.13 (2)
E	—	—	47 (2)	—	—	1.14 (2)
One twin sacrificed (E); one left alive (C):						
204E	875	46	—	1.65	0.46	0.46 (2)
C	519	494	—	1.77	0.99	1.87 (2)
41E	667	259	87 (3)	2.67	0.83	0.83 (3)
C	523	615	694 (3)	1.92	1.51	1.32 (3)
35E	934	190	—	1.88	0.69	0.62 (4)
C	793	506	—	1.85	1.62	1.71 (4)
B10* E	—	—	49 (2)	—	—	1.70 (2)
C	—	—	289 (2)	—	—	2.80 (2)

*Estimated by scheme described in appendix except animals B14 and B10 in which uterine blood flow was estimated by direct Fick method.

and progestins have an important role in regulation of uterine blood flow at different times in reproductive cycles, we examined the data from experiments in which the fetus was alive for relationships which might be useful in future study of the problem. The correlation between total blood flow to the uterus (milliliters per minute) and plasma concentrations of estradiol was 0.61 ($n = 11$, $p < 0.05$), and between total blood flow and progestins was 0.363 ($n = 16$, $p > 0.05$). The correlation betweeen the rate of uterine blood flow (milliliters per kilogram per minute), as measured by the diffusion equilibrium method, and the ratio of the concentration of estradiol to progestins was 0.404 ($n = 9$, $p > 0.05$). Though some of these relationships were suggestive, none was convincing.

The change in uterine blood flow (milliliters per minute) which followed fetal death appeared to occur in advance of changes in concentrations of either hormone; progestin concentrations decreased proportionately within 2 hours but estradiol hardly changed. In fact, there was a suggestion that it temporarily increased (Fig. 4).

These experiments did not demonstrate a significant relationship between blood flow to the pregnant uterus and A-V O_2 and concentration of estradiol and progestins in maternal plasma. However, they do not eliminate the possibility that any one of them may have an important regulatory role. For example, it is conceivable that prolonged exposure to lowered oxygen may stimulate growth of the uterine vascular bed. Similarly, uterine blood flow may be related to some facet of steroid metabolism not studied in these experiments, e.g., rates of hormone production or their concentrations in target tissues.

The physiologic significance of tissue concentrations of hormones is particularly intriguing because the changes in the uterine circulation following fetal death appeared to relate best to changes within the uterus, specifically to deterioration of the chorioallantoic membrane. We had no way to quantitate this relationship but the inference is supported by experiments in which one of a set of twins was killed; the morphologic, metabolic, and circulatory changes tended to be unilateral, confined to the horn with the dead fetus. The uterine vasculature presumably was responding either to a maternal stimulus capable of producing a local response or to a stimulus local both in its origin and its effects. Since hormones are released by the choriallantoic membrane and they are capable of acting locally, the second alternative is most attractive. This question is under study.

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Appendix

In using the Fick method to measure total blood flow (milliliters per minute) to the uterus, antipyrine is infused into a central vein for 5 minutes. Coincident with the start of the infusion and continuing for 15 minutes thereafter, arterial and uterine venous bloods are sampled at a constant rate. At the end of that time a second set of blood samples is drawn as rapidly as possible; the uterus and its contents are excised and weighed. Antipyrine is extracted from all tissues and fluids and measured (A_{tiss}, in milligrams). With these data flow (milliliters per minute) is calculated by the formula

$$\frac{A_{tiss} \times 100}{(A_a - A_v) \times 20 \text{ min.}}$$

in which (Aa − Av) is the difference between antipyrine concentration (in milligrams per 100 ml.) in arterial and uterine venous blood sampled continuously over 20 minutes. As the uterus is excised only one measurement may be made on each animal.

Repeat determinations of blood flow (milliliters per minute) may be obtained if an *estimate* of the total amount of antipyrine within the uterus is substituted for the *measurement* of A_{ttss}. Such is possible when the fetus is alive and the ewe free from apparent stress, because the change in concentration of antipyrine in

Table III. Comparison of measurements and estimates of the total amount of antipyrine contained within the uterus

	1	2	3	4	5	6
	Antipyrine content				*Uterine blood flow (ml./min.)*	
Sheep	*Measured*	*Predicted*	*Measured as per cent of predicted*	*Aa-Av antipyrine (mg./100 ml.)*	*Fick*	*Estimate*
Alive:						
B53	160.4	149.7	94.8	0.67	1,197	1,117
B30	107.4	113.4	94.7	0.75	716	754
B16	128.1	125.4	102.1	—	—	—
R53	41.2	38.3	107.6	0.69	298	277
$\bar{X}$ ± S.E.M. = 99.8 ± 3.1						
Dead 20 min.:						
240	45.1	61.6	61.6	0.28	796	555
N.T.	29.9	66.4	66.4	0.28	690	646
Y238	35.8	71.0	71.0	0.22	570	560
Y236	42.2	57.9	57.9	0.36	670	563
Dead 110 min.:						
Y37	26.8	52.1	52.1	1.05	127	129
B14	15.1	65.2	65.2	1.19	81	139
W67	19.0	50.4	50.4	1.20	79	106
Y229	19.2	30.0	30.0	0.56	125	135
W28	34.5	69.5	69.5	0.36	510	486
Dead 230 min.:						
Y36	17.2	44.9	38.3	1.30	129	78
Y61	27.3	49.9	54.7	0.85	154	132
Y59	28.3	52.2	54.2	0.27	538	489
Y246	24.9	41.9	59.4	1.58	79	67
$\bar{X}$ ± S.E.M = 50.6 ± 3.8						

uterine venous blood before and immediately after the 20 minute flow determination ($Auv_{20} - Auv_0$) has been shown to be closely related to the change in average concentration (milligrams per 100 ml.) in water of various tissues contained within the uterus. If these tissues (fetus, placenta, and uterus) are excised at the end of the experiment, their combined weight may be multiplied by the measurement of $Auv_{20} - Auv_0$—from each flow determination—to substitute for A_{tiss} in the formula given above and thus estimate total flow (milliliters per minute).

The scheme described above is satisfactory tc estimate uterine blood flow (milliliters per minute) when the fetus is alive and it was used in such circumstances. If used after the death of the fetus, however, it was unsatisfactory. In this situation, the product of $Auv_{20} - Auv_0$ and the combined weights of fetus, placenta and uterus (Table III, Col. 2) overestimated the total amount of antipyrine actually contained within the uterus (Table III, Col.1). The difference was related to two factors, both of which were a consequence of fetal death. First, no antipyrine entered fetal tissues—a situation which had been anticipated. Second, the myometrium and placenta fell short of an equilibration with antipyrine in uterine venous blood at 20 minutes (uv_{20}) (Table II). Moreover, the amounts in amniotic and allantoic fluids were less, far short of the amount needed to cancel the deficit (as it does when the fetus is alive). If fetal weight were excluded, the difference between *predicted* (uv_{20} × kilogram of uterus and placenta) and *measured* amounts of antipyrine (Table III, Cols. 1 and 2) when the fetus was dead, appeared to be regular as the latter were, on the average, 50.6 ± 3.0 (S.E.M.) of the former (Col. 3). On this basis, we explored the possibility of "predicting" tissue content when the fetus was dead by systematically taking 50.6 per cent of the product of weight (placenta and uterus—kilogram and $Auv_{20} - Auv_0$) and substituting this in the Fick equation. The results of this calculation are given in Table III, Col. 6. The relationship between this estimate (y) and that obtained by direct Fick (x) (Col. 5) is given by the formula

$$y = -0.65x + 35$$

Since the correlation between estimates was good ($r = 0.95$), we used this modification to estimate A_{tiss} in those determinations of uterine blood flow (milliliter per minute) on the second group of animals made after the fetus had been killed.

Malignant nephrosclerosis during pregnancy and in the postpartum period (the uremic hemolytic syndrome)

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Histologic, immunohistologic, and ultrastructural features are presented of two cases with malignant nephrosclerosis during pregnancy. Primary malignant nephrosclerosis emerges as a clinical entity which can be distinguished from toxemia of pregnancy in the midtrimester and post partum.The first description of malignant nephrosclerosis dates from 40 years ago, but only a few cases were reported associated with pregnancy. Although disseminated intravascular coagulation seems involved, the morphology is different from that of toxemia. Malignant nephrosclerosis reveals a close similarity to the hemolytic uremic syndrome. Early diagnosis by renal biopsy and proper treatment may prevent a lethal outcome due to progressive renal failure.

THE TERM "malignant nephrosclerosis" refers to a distinct renal disease which is diagnosed by renal biopsy. Evidence suggests that the pathogenesis and morphology of malignant nephrosclerosis are similar to those of the hemolytic uremic syndrome.[1] Additional terminology, such as "thrombotic microangiopathy," is confusing and will be discussed later. Both malignant nephrosclerosis and the hemolytic uremic syndrome have been described in association with abortion, pregnancy, the postpartum period, and oral contraceptives. The clinical symptomatology is easily confused with pre-eclampsia. To rule out the latter is mandatory, since toxemia is a benign disease as far as prognosis is concerned, whereas malignant nephrosclerosis progresses in many instances to death.

During 1973 we have observed two cases of malignant nephrosclerosis, one during pregnancy and one post partum. A third case was not related to pregnancy, indicating that this disease may also occur without connection with pregnancy. Clinical, histologic, and immunohistologic examinations of this case served as positive controls. The paper presented deals with clinical, histologic, immunochemical, and ultrastructural features of malignant nephrosclerosis.

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Case reports

Case 1. I. S. U. was a 33-year-old woman, para 3-0-0-3. The last menstrual period (LMP) was on March 25, 1972, and the estimated date of confinement (EDC) was December 30, 1972. Proteinuria and red blood cells in the urine were encountered in September, 1972. The patient was treated conservatively and delivered in another hospital on December 31, 1972. Diagnosis was made of mild toxemia. Three weeks post partum generalized edema developed and the patient became anuric, which prompted admission to the University Hospital (Fig. 1).

Laboratory values on admission were as follows. Serum creatinine was 1 mg. per 100 ml.; uric acid, 14.2 mg. per 100 ml.; serum lactic dehydrogenase (LDH), 438 mU. per milliliter; proteinuria, 5 Gm. per 24 hours; hematocrit (Hct.), 7.4 mg. per cent; erythrocytes

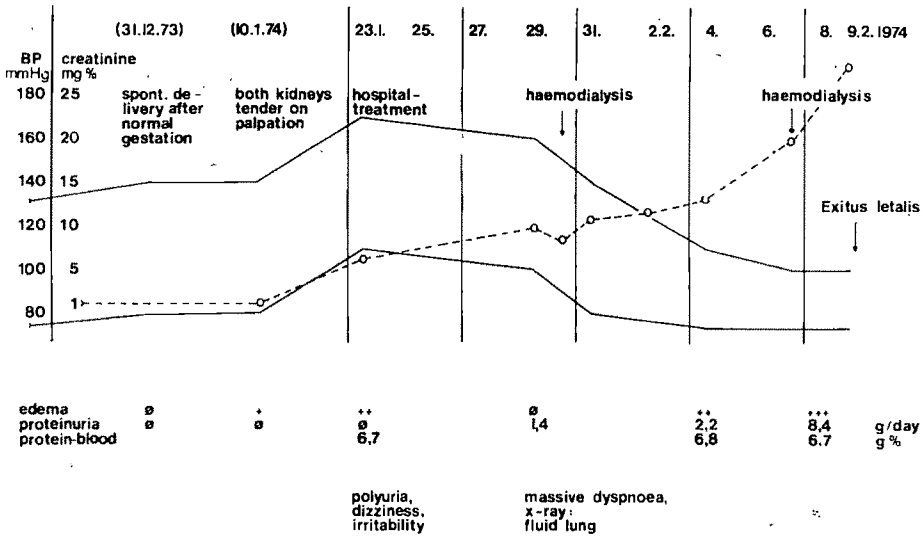


Fig. 1. Clinical case of Patient I. S. U., 33 years of age, para 3-0-0-3.

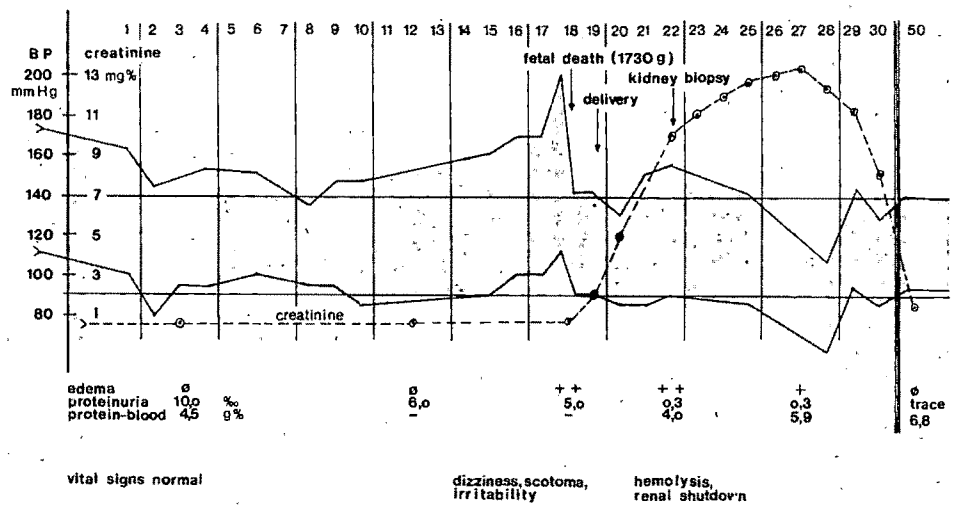


Fig. 2. Clinical case of Patient R. B., 33 years of age, para 4-3-0-0, in week 34 of gestation.

(Ery.), 2.4 million; white count, 8,200 per cubic millimeter, normal distribution; red cell sedimentation rate, 120/153; blood pressure, 140/80 mm. Hg. Circulating autoantibodies against lung and kidney tissue could not be demonstrated. The patient underwent immediate dialysis, which had to be repeated 10 days later. She became dyspneic at the second dialysis and died from massive pulmonary hemorrhage and edema.

Case 2. R. B., 33-year-old woman, para 4-3-0-0, was admitted to the University Hospital with the diagnosis of pre-eclampsia following normal prenatal care on September 18, 1973. LMP was on January 27, 1973; the EDC was November 2, 1973. Systolic hypertension of 170/80 and proteinuria were observed in the second trimester but the patient had no edema and hyperreflexia (Fig. 2). A diagnosis of pre-eclampsia was made. The plan was to deliver the patient prematurely at week 38. Intrauterine death occurred on October 6, 1974, with subsequent spontaneous labor and delivery. Instead of improvement after delivery the patient went into renal failure on the third day post partum with signs of hemolysis. The clinical diagnosis was changed to hemolytic uremic syndrome. The patient was treated with intravenous heparin. She received doses of 20,000, 10,000, and 10,000 I.U. at 8 A.M., 1 P.M., and 7 P.M., respectively, for 14 days. The patient left the hospital on November 6, 1973 in good condition with normal kidney function.

Laboratory findings on admission were as follows. Hct., 11.8 mg. per cent; Ery., 4 million; white count, 5,000 per cubic millimeter (normal distribution); platelets, 160,000 per cubic millimeter; Esbach, 11 per cent;

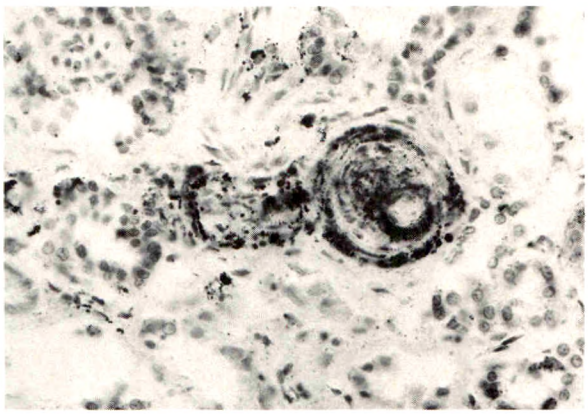


Fig. 3. Kidney histology of malignant nephrosclerosis with massive incorporating of lipids in an arteriole with wall sclerosis and obstruction of the lumen. (Hematoxylin and eosin; original magnification ×350.)

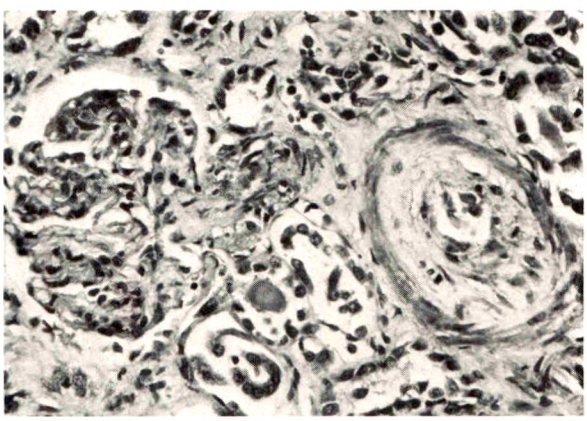


Fig. 4. Kidney histology: Note the intima enlargement of the capillary with onion shell appearance. The glomeruli reveal swollen loops. The fibrinoid incorporation extends in some instances from the arterioles to the afferent vessel. The interstitium is edematous. The tubulus cells are slightly atrophic without presence of necrosis. (Hematoxylin and eosin; original magnification × 300.)

glucose tolerance test, 69 to 118 mg. per 100 ml.; serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase, normal; bilirubin, 0.33 mg. per 100 ml.; blood urea nitrogen (BUN), 57.9 mg. per 100 ml.; serum creatinine, 0.88 mg. per 100 ml.; electrolytes, within normal limits. Repeated serum examinations for circulating autoantibodies against lung and kidney tissue were negative

Laboratory findings on October 10, 1973 included the following. Hb., 59 per cent; Ery., 2.9 million; white count, 6,000 per cubic millimeter. There were schistocytes in the blood smear. The blood pressure (BP) was 240/120 mm. Hg; serum creatinine, 13.05 mg. per 100 ml.; urea, 112 mg. per 100 ml.; uric acid, 13.5 mg. per 100 ml.; LDH, 1,395 M.E. per

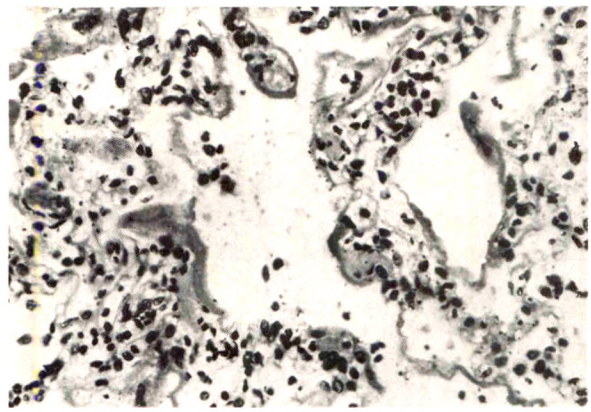


Fig. 5. Hyaline membranes in lung alveoli (Patient I. S. U.). (Hematoxylin and eosin; original magnification × 400.)

milliliter; serum bilirubin and alkaline phosphatase, normal. Proteinuria was 2 Gm. per 24 hours and there were multiple red cells in the urine.

Histology

The primary abnormality concerned the arterioles: some of them revealed an enlargement of the intima by incorporation of fibrinoid substance which was periodic acid–Schiff (PAS) positive. In some instances the material was depositied also in the media. Partial obliteration by intima proliferation was observed and in other arterioles disintegration of the intima. Sudan III stain revealed small drops in all parts of the fibrinoid material, often clumped in small groups (Figs. 3 and 4). Interstitial edema was seen in the cells of the tubules, which were slightly atrophic without necrosis. Landry's stain revealed fibrin deposition in the renal capillaries.

Hemorrhagic edema was present in the lung of patient 1. Massive hyaline membranes were combined with fresh fibrin thrombi (Fig. 5).

Immunofluorescence

In kidney sections of both patients, nearly all glomeruli, especially the afferent vessels and small kidney arteries, showed bright diffuse fluorescence, following staining with fluorescein-labeled antifibrinogen serum (Fig. 6, *A*). The stain was present throughout the glomerulus, focal granular deposits being frequently observed at the glomerular basement membrane (Fig. 6, *B*).

The small lung arteries revealed also bright fluorescence after staining with fluorescein-conjugated antifibrinogen serum (Fig. 7, *A*). In addition, staining was observed along the alveolar walls (Fig. 7, *B*).

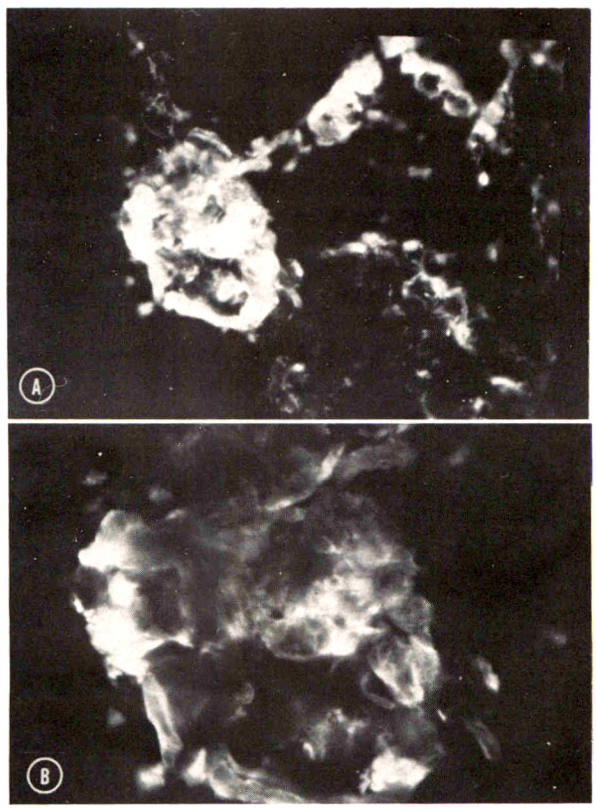


Fig. 6. Immunofluorescence. Section of renal tissue from Patient I. S. U. Staining with fluorescein-conjugated rabbit antiserum to human fibrinogen. Note the bright fluorescence of the golmerulus, afferent vessel, and small renal artery. (A, original magnification × 80; B, original magnification × 150.)

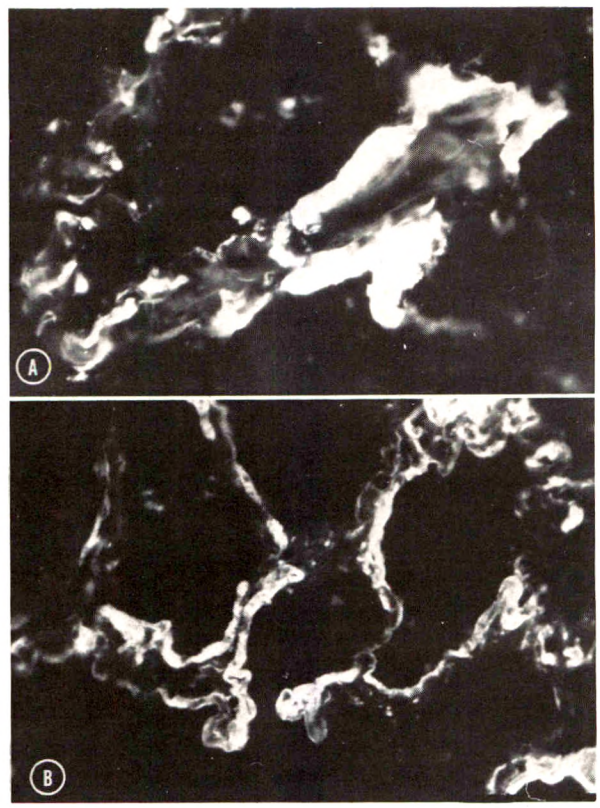


Fig. 7. Immunofluorescence. Section of pulmonary tissue from Patient I.S.U. Staining with fluorescein-conjugated rabbit antiserum to human fibrinogen. Note the fluorescence of small artery and alveolar wall. (*A*, original magnification ×80; *B*, original magnification ×150.)

In contrast to these findings, all control experiments using fluorescein-labeled antisera directed against immunoglobulins G, M, A and complement components gave negative results.

Electron microscopy

The major ultrastructural alteration in the kidneys examined concerned the glomerular capillary loops and afferent arterioles. Edematous intima was combined with deposition of fibrin, endothelial swelling, and necrosis. Proliferative changes of the intima were frequently observed, with scarring of the vessel wall. There was proliferation of the mesangial cells and the mesangial matrix as well as swelling and proliferation of endothelial cells. Splitting of the basement membrane was frequently associated with incorporated mesangial cells. Electron-dense deposits were localized within the basement membrane which could correspond to fragmented erythrocytes. Capillaries frequently contained polymorphonuclear leukocytes. Large parts of the glomerular loops were completely obliterated (Figs. 8 and 9).

Comment

The disease entity of malignant nephrosclerosis was first described by the German pathologist Far[2] in 1916. There have been lengthy discussions over the past 40 years on whether the kidney pathology results from chronic hypertension or the high blood pressure results from the kidney disease.

Bohle and associates[1] evaluated recently more than 50 cases and compared clinical symptomatology with kidney pathology. It seems apparent from these data that there are two disease entities with similar morphology. The clinical course, in what Bohle and associates[1] call *primary* malignant nephrosclerosis, begins with a slow increase in blood pressure, subsequent proteinuria, hemolysis, and spherocytosis. *Secondary* malignant nephrosclerosis is associated with long-standing hypertension. The differentiation of these two disease entities can clarify the various terms described in the literature.

The hemolytic uremic syndrome described by Gasser and associates[3] in 1955 has some features similar to primary nephrosclerosis. There is evidence to assume

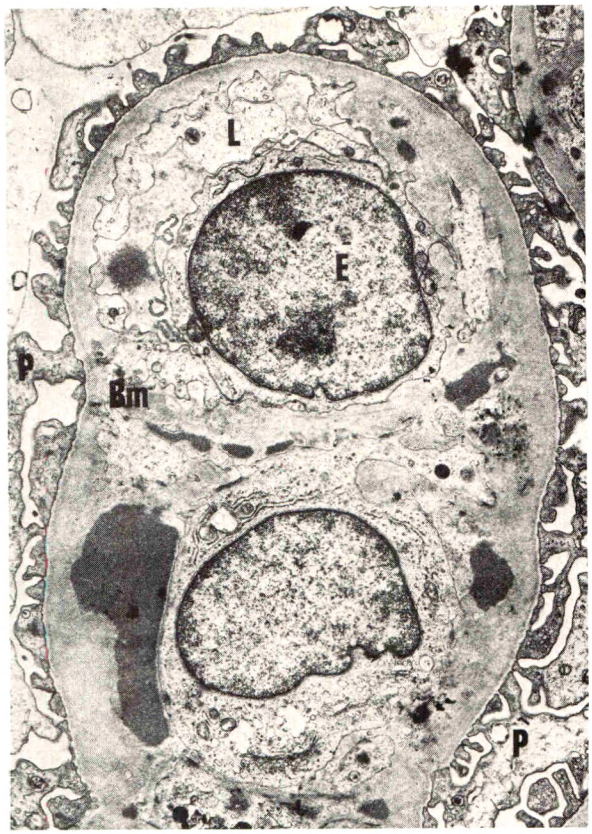


Fig. 8. Ultrastructure of the glomerulus. The glomerular capillary is nearly completely occluded. A rest lumen can be seen in the upper half of the picture. Bridges of basement membrane material obliterate the lumen. There are several electron-dense areas which may be fragments of erythrocytes. *L* = capillary lumen; *E* = endothelial cell; *Bm* = basement membrane; *P* = podocytes. (original magnification ×6,600.)



Fig. 9. Ultrastructure of the glomerulus. Glomerular capillary with associated mesangium cells. Note the splitting of the basement membrane with incorporated cell parts. There is swelling of the endothelial cells. A neutrophilic granulocyte is seen in the center. The mesangium is enlarged by cell proliferation. Description as in fig. 8. (Original magnification ×7,200.)

that cases of thrombotic thrombocytopenic purpura are rather cases of primary nephrosclerosis.[4, 5] Brain and associates[6] introduced the term microangiopathic hemolytic anemia for a group of diseases which included, for instance, the hemolytic uremic syndrome, polyarteritis nodosa, and some cases of malignant hypertension. McKay[7] recently presented evidence that patients with toxemic eclamptic convulsions also belong to this group, whereas pre-eclampsia does not reveal spherocytosis. It is believed that "helmet cells" and microspherocytes are associated with fibrin strands in the microcirculation.[6] Microangiopathic hemolytic anemia seems, therefore, just another expression of pronounced disseminated intravascular coagulation. It is felt by this group that the diagnosis of any kidney disease should be based on a specific morphologic lesion, whereas the hemolytic uremic syndrome refers to a description of clinical symptoms. We therefore support the term primary nephrosclerosis.

Primary malignant nephrosclerosis, the uremic hemolytic syndrome, and thrombotic microangiopathic renal lesions are disease entities, which were observed post partum and occasionally diagnosed in pregnancy[4, 6, 8–16] and after the use of oral contraceptives.[17, 18] The pathognomonic role of pregnancy is as yet unknown.

For the clinician familar with toxemia the symptomatology of malignant nephrosclerosis appears similar and, indeed, differential diagnosis can be obtained only by renal biopsy. The mild pre-eclampsia in a few cases described[8, 12, 14] seems to be part of the disease and not an additional complicating factor. The cases presented by Sarles and associates[18] and Rosemann and associates[5] presumably suffered from malignant nephrosclerosis. The benefit of renal biopsy for the patient is obvious, since toxemia is a benign, self-limiting disease, whereas primary malignant nephrosclerosis can be lethal. It is not yet clear, whether primary malignant nephrosclerosis is a systemic dis-

ease, as in our patient 1, or limited to the kidney, as in other patients.

Clinically, Epstein and associates[19] considered as differential diagnosis rapidly progressive, coexistent glomerulonephritis, lupus erythematosis, Goodpasture's syndrome, and, finally, hypersensitivity vasculitis. Whereas for most of these diseases autoimmune reactions are of importance, the etiology of primary malignant nephrosclerosis is still unknown.

Tests for circulating antibodies against kidney tissue are negative. Characterisitc is the Coombs negative hemolytic anemia and the presence of schistocytes and helmet cells and an increase in serum LDH. Thrombocytopenia has been described in some cases, whereas coagulation factors are normal and in some instances high concentrations of fibrin-fibrinogen degradation products were observed[21] which failed to be present in others.[22]

The histology of malignant nephrosclerosis is characteristic. One significant finding is early fibrinoid swelling, necrosis, and lipoidosis of the preglomerular arterioles. Necrosis extends often to the initial glomerular loops. Changes in the glomerular apparatus have to be considered as a secondary phenomenon. In contrast the kidney lesion, believed to be specific for pre-eclampsia, is characterized by endothelial swelling of the glomerular capillary (so-called endotheliosis) and occasionally arteriolar necrosis. Glomerular capillary thrombosis, as identified by fibrin stains, is mostly seen in kidneys of patients who have died in eclamptic seizure.[7]

Careful studies of the histology and ultrastructure presented in the literature and comparative studies of one case of primary malignant nephrosclerosis not related to pregnancy revealed that the lesion is identical in pregnant and nonpregnant patients. Especially specific histologic changes of toxemia in pregnancy as described above were not present in the two cases observed. The term superimposed toxemia is therefore not applicable on morphologic grounds.

The morphology of malignant nephrosclerosis is not identical with that of the generalized Schwartzman reaction, although the presence of fibrin deposits was noted. The lesion is indistinguishable by immunofluorescent staining from toxemia lesions as described by Morris and associates.[23] The positive fluorescent staining with an antihuman fibrinogen antiserum seems not to be disease specific. Presence of schistocytes is in accordance with the assumption of involvement of disseminated intravascular coagulation.

The basic treatment presently used is fluid and electrolyte balance, high-caloric and low-protein diet, antihypertensive treatment, and hemodialysis if needed. In spite of some good results, at least one third of patients die of renal failure.

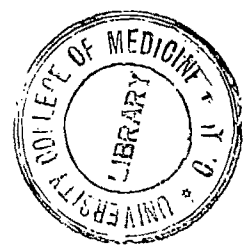
Treatment with heparin was attempted but in most instances met with failure.[8, 10, 13, 21] The positive results described by some authors[14, 16, 24] as well as one of our cases should be considered with care in regard to the rareness of the disease and lack of controlled studies. In two instances fibrinolytic therapy with streptokinase was attempted without success.[12, 20]

Primary malignant nephrosclerosis has been described for the last 2 years with increasing frequency. This may be related to new diagnostic means in nephrology. The disease does not seem to be as infrequent as previously reported and should be considered in the differential diagnostic consideration of toxemia in pregnancy.

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Hyperuricemia in pre-eclampsia

A reappraisal

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Seventeen pre-eclamptic (PE), 22 hypertensive (H), and 13 normal pregnant women (C), all in the third trimester, were studied to examine the relationship of blood lactate (L) to the hyperuricemia characteristic of PE. The parameters measured were: serum and urinary uric acid, and creatinine, and lactate (L), and pyruvate (P) in the blood. Uric acid clearance (C_{ur}), and creatinine clearance (C_{cr}), and fractional uric acid clearance (Fract. C_{ur}) as well as L/P ratios were calculated. Some of the patients, from the three groups, were infused with ≅ 100 mEq. of sodium lactate during the course of 50 minutes. "Preinfusion," "midinfusion," and "postinfusion," determinations were compared, as well as the per cent change in the different parameters as the result of the infusion and after its discontinuation. The results showed that serum uric acid is elevated, and C_{ur} is impaired in PE; however, L was lower in PE than in control subjects. There was no correlation between L or L/P and C_{ur}. Lactate infusion caused comparable impairment of C_{ur} in all groups. There was no significant difference in the response of the parameters studied, to the infusion, between the different groups. Our data cast serious doubts on the postulated role of blood lactate in the etiology of hyperuricemia in PE. Contracted plasma volume and/or local release of angiotensin II in the kidney of pre-eclamptic patients probably play a more important role.

IN PRE-ECLAMPTIC patients (PE) with mild pathologic lesions documented by renal biopsy, serum uric acid (SUA) was elevated before other nitrogenous end products.[1] In more severe cases, when the latter are elevated, SUA is disproportionately higher.[2] In chronic hypertensive disease complicating pregnancy SUA may be elevated but usually to the same degree as other nitrogenous end products. This led to the suggestion that the ratio of SUA to blood urea, nonprotein nitrogen, or blood urea nitrogen could help in differentiating pre-eclamptic from hypertensive pregnant women.[1–4]

The pathogenesis of hyperuricemia in PE has not as yet been determined. The possibility of overproduction of uric acid by the fetoplacental unit has not been proved[5, 6] and the suggestion that it is due to decreased hepatic degradation has been discarded.[7] Intestinal uricolysis, which normally accounts for about 30 per cent of uric acid disposition, has not been studied in PE. Generally accepted are the facts that both the glomerular filtration rate (GFR) and uric acid clearance (C_{ur}) are impaired in PE.[7, 8] However, that the former is the only cause for the latter is unlikely because C_{ur} was reduced to a greater extent than was the GFR.[7] At the same time it was realized that filtered urate is mostly reabsorbed by the proximal tubules and the bulk of excreted urate is the result of secretion by the renal tubules. It was therefore postulated that decreased C_{ur} is the result of enhanced tubular reabsorption, or inhibited tubular secretion, or both.[1]

Evidence has accumulated that elevated blood lactic acid levels interfere with uric acid excretion.[9] Hyper-

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Table I. Summary of the clinical data of the patients studied

	Age (yr.)	*Parity*	*Gestational age (wk.)*	*Mean BP (mm-Hg)**
Normal pregnancy	16-25	0-4	30-40	84.7
(13)†	20.62 ± 2.9	2	36.0 ± 3.44	
Hypertension	16-41	0-9	32-41	114.1
(22)†	26.41 ± 6.3	2	38.09 ± 2.02	
Pre-eclampsia	16-24	0	31-41	109.7
(17)†	19.18 ± 2.16		36.76 ± 2.49	

*Mean BP = diastolic pressure + one-third pulse pressure.

†Number of patients studied.

Table II. Comparison of the means of different determinations in the three groups of patients studied

	Normal pregnancy "C" (13 patients)	*Hypertension "H" (22 patients)*	*Pre-eclampsia "PE" (17 patients)*	*D**	*Remarks*
Serum uric acid (mg./100 ml.)	4.17	5.45	6.66	0.76	Significant difference between all groups
Uric acid clearance (ml./min.)	14.03	9.88	7.19	2.234	Significant difference between all groups
Serum creatinine (mg./100 ml.)	0.68	0.71†	0.77	0.66	Significant difference between PE and C
Creatinine clearance (ml./min.)	159.76	135.25†	121.62	12.49	Significant difference between all groups
Fractional uric acid clearance (ml./100 ml. GFR)	8.86	7.62†	5.84	1.32	Significant differences between C and PE; H and PE
Blood lactate (mmol/L.)	1.145	0.930	1.076	0.018	Significant differences between all groups
Blood pyruvate (mmol/L.)	0.138	0.104	0.133	0.021	Significant differences between C and H; H and PE
Lactate/pyruvate ratio	9.82	9.24†	8.42	2.44	No significant differences between any of the groups

*D = Least significant difference between groups at the 5 per cent level, "Tukey's test for multiple comparisons."

†Observations made in 21 patients only.

lactacidemia was reported in toxemia of pregnancy.[10] Handler[11] concluded that high blood lactic acid levels in PE result in selective impairment of C_{ur}. This theory has become generally accepted[4] without sufficient evidence.

The present study was designed to re-examine the relationship between lactic acid and uric acid in PE and hypertensive disease with pregnancy.

Materials and methods

Third-trimester pregnant women were assigned to one of three groups. *(1) control (C):* 13 healthy pregnant women without a history or evidence of either hypertensive or renal disease; their blood pressure did not exceed 120/80 mm. Hg during the current pregnancy. *(2) chronic hypertension (H):* 22 patients who were hypertensive during a previous pregnancy or who had their hypertension detected before the twentieth week of gestation; *(3) pre-eclampsia (PE):* 17 primigravidas without a history of hypertension prior to their pregnancy and who were normotensive during the first half of pregnancy; after 30 weeks of gestation they manifested hypertension with or without edema and/or proteinuria; the hypertension was defined as an increase of 30 mm. Hg systolic pressure and/or 15 mm. Hg diastolic pressure, over previous determinations, that persisted after 6 hours of bedrest.

The protocol of the study was explained to the patients and informed consent was obtained. Only water was permitted between midnight and 7:00 A.M. At 7:00 A.M. a Foley catheter was inserted and the patient was placed in the lateral decubitus position for the study period. Oral fluid consumption of 150 to 200 ml. of water every 15 minutes was maintained until urinary flow became adequate. The water intake was subsequently regulated to replace the urinary loss so

Table III. Effects of lactate infusion* in five normal pregnant women

	Preinfusion	*Midinfusion*	*t*	*Per cent change*
Serum uric acid (mg./100 ml.)	4.64† ± 1.35	4.91† ± 1.71	t = 0.251 N.S.	105.33‡ ± 11.29
Uric acid clearance (C_{ur}) (ml./min.)	12.44 ± 3.75	2.76 ± 1.21	t = 4.916 <0.002	21.53 ± 4.63
Serum creatinine (mg./100 ml.)	0.72 ± 0.11	0.72 ± 0.12	t = 0 N.S.	100.7 ± 7.89
Creatinine clearance (C_{cr}) (ml./min.)	143.78 ± 19.2	140.56 ± 36.16	t = 0.172 N.S.	97.23 ± 14.55
Fractional uric acid clearance $\left(\frac{C_{ur}}{C_{cr}} \times 100\right)$	8.8 ± 2.8	2.13 ± 1.32	t = 4.311 <0.01	23.18 ± 9.41
Blood lactate (L) (mmol/L.)	1.209 ± 0.259	2.278 ± 0.266	t = 5.65 <0.001	193.59 ± 34.94
Blood pyruvate (P) (mmol/L.)	0.167 ± 0.036	0.224 ± 0.067	t = 1.524 N.S.	141.23 ± 54.86
L/P ratio	7.286 ± 0.842	11.22 ± 5.034	t = 1.542 N.S.	151.62 ± 53.74

*Intravenous infusion of ≅ 600 ml. of 1/6M. sod. lactate over 50 minutes.
†Mean ± S.D.
‡Mean ± S.D. of the per cent of change over preinfusion values in each individual patient.

Table IV. Effects of lactate infusion* in hypertensive patients

	Preinfusion	*Midinfusion*	*t*	*Per cent change*
Serum uric acid (mg./100 ml.) (10)†	5.86‡ ± 1.39	5.86‡ ± 1.34	t = 0.006 N.S.	100.17§ ± 4.34
Uric acid clearance (C_{ur}) (ml./min.) (10)	10.72 ± 4.08	2.51 ± 1.87	t = 5.493 <0.001	17.8 ± 9.244
Serum creatinine (mg./100 ml.) (9)	0.76 ± 0.21	0.74 ± 0.18	t = 0.166 N.S.	98.77 ± 6.05
Creatinine clearance (C_{cr}) (ml./min.) (9)	136.89 ± 35.11	119.39 ± 20.67	t = 1.215 N.S.	89.93 ± 16.74
Fractional uric acid clearance (9) $\left(\frac{C_{ur}}{C_{cr}} \times 100\right)$	8.52 ± 1.98	2.22 ± 1.36	t = 7.422 <0.001	25.82 ± 15.05
Blood lactate (9) (L) (mmol/L.)	1.036 ± 0.391	1.743 ± 0.761	t = 2.338 <0.05	175.22 ± 66.52
Blood pyruvate (10) (P) (mmol/L.)	0.115 ± 0.02	0.149 ± 0.028	t = 3.4 <0.01	130.48 ± 18.72
L/P ratio (9)	8.749 ± 2.341	11.294 ± 3.337	t = 1.752 N.S.	133.69 ± 42.58

*Intravenous infusion of 600 ml. 1/6M sod. lactate over 50 minutes.
†Numbers in parentheses are the number of observations.
‡Mean ± S.D.
§Mean ± S.D. of the per cent change over preinfusion values in each individual patient.

that a steady flow was maintained. Blood was collected from an unconstricted vein so that lactic and pyruvic acid levels would approximate the corresponding arterial blood levels.

Three urine collection periods of 20 minutes each were made with blood samples obtained in the middle of each period. Great care was taken to remove all urine from the bladder by applying suprapubic pressure, rinsing the bladder with sterile water, and instilling air to displace all the washout fluid.

The effect of a sodium lactate infusion was studied in some of these patients. Following the three urine collection periods, 1/6M. sodium lactate was infused into the other arm with an infusion pump. About 600 ml. of the solution (≅100 mEq. of sodium lactate) was delivered in 50 minutes. Urine excreted during the initial 10 minutes was discarded and two 20 minute collection periods followed. Two additional 20 minute urine samples were collected after discontinuation of the intravenous infusion. Blood samples were drawn in the middle of each of the collection periods. Urine volumes as well as urinary uric acid and creatinine content were determined. Uric, lactic, and pyruvic acids and creatinine levels in all blood samples were measured. Endogenous creatinine and uric acid clearances were calculated according to the formula

Postinfusion	*t*	*Per cent change*
5.21† ± 1.78	t = 0.513 N.S.	111.94‡ ± 11.75
4.12 ± 3.63	t = 3188 <0.02	31.69 ± 19.79
0.71 ± 0.17	t = 0.099 N.S.	98.41 ± 12.19
133.79 ± 21.94	t = 0.685 N.S.	92.87 ± 7.71
3.16 ± 2.41	t = 3.051 <0.02	34.03 ± 19.97
1.991 ± 0.298	t = 3.896 <0.01	172.17 ± 45.58
0.215 ± 0.056	t = 1.45 N.S.	133.22 ± 39.75
9.734 ± 1.884	t = 2.373 <0.05	134.08 ± 22.41

Postinfusion	*t*	*Per cent change*
5.82‡ ± 1.26	t = 0.074 N.S.	99.84§ ± 5.81
3.6 ± 3.6	t = 3.926 <0.001	28.94 ± 20.85
0.78 ± 0.21	t = 0.193 N.S.	102.68 ± 4.54
135.98 ± 42.56	t = 0.046 N.S.	98.95 ± 12.88
2.87 ± 2.59	t = 4.907 <0.001	31.69 ± 22.85
1.534 ± 0.793	t = 1.596 N.S.	152.55 ± 68.23
0.126 ± 0.024	t = 1.1 N.S.	111.64 ± 21.364
12.519 ± 7.419	t = 1.371	147.69 ± 85.96

Cl = (UV/P). All clearances were then corrected to a body surface area of 1.73 sq. m. For the infusion study, the three baseline collection periods were averaged together as "pre-infusion," the two periods during the infusion were averaged as "mid-infusion," and the last two collection periods after discontinuation of the infusion as "postinfusion."

Enzymatic analysis for blood lactate and pyruvate were performed on trichloracetic acid plasma free filtrates with lactic dehydrogenase and the dinucleotide cofactor (Sigma Technical Bulletin, 627/826-UV). Creatinine in the serum and the urine were measured by the method of Teger-Nilsson.[12] Uric acid in the serum was determined by an enzymatic colorimetric method (Sigma Technical Bulletin, 680). All determinations were run in duplicate. Statistical analysis of the data was done with Tukey's multiple comparison test, Student's t test, and correlation analysis.[13]

Results

The clinical data of the patients are summarized in Table I. The results of the different determinations; SUA, C_{ur}, serum creatinine, creatinine clearance (C_{cr}), fractional uric acid clearance (Fract. C_{ur}), lactate (L), pyruvate (P) and L/P ratio are given in Table II.

Tukey's test for multiple comparison was used for statistical analysis. This test has the capability of estimating the significance of differences between any two of multiple groups. SUA was significantly higher in PE (5.66 mg. per 100 ml.) than in both the controls (4.17 mg. per 100 ml.) and the hypertensive pregnant women (5.45 mg. per 100 ml.). In the latter, SUA was also significantly higher than in the controls. There was significant reduction of C_{ur} in both PE (7.19 ml. per minute) and H (9.88 ml. per minute) as compared to controls (14.03 ml. per minute). However, C_{ur} was significantly more reduced in PE than in H. The serum creatinine was significantly higher in PE (0.77 mg. per 100 ml.) than in the controls (0.68 mg. per 100 ml.). The serum creatinine in H (0.7 mg. per 100 ml.) was not significantly different from either PE or controls. C_{cr} was significantly impaired in PE (121.62 ml. per minute) as compared to normal pregnancy (159.76 ml. per minute). In hypertensive pregnant women C_{cr} was significantly impaired (135.25 ml. per minute). The degree of impairment was less than in PE. The difference between PE and H was significant. Fract. C_{ur} is decreased in H (7.62 ml. per 100 ml. GFR) and to a greater extent in PE (5.84 ml. per 100 ml. GFR) as compared to controls (8.86 ml. per 100 ml. GFR). The differences between the pre-eclamptic and both the control and hypertensive groups were significant. Blood lactate was lower in both H (0.93 mmol per liter) and PE (1.076 mmol per liter) than in controls (1.145 mmol per liter). The differences between all groups were significant. Blood pyruvate was lower in H (0.104 mmol per liter) than in both the controls (0.138 mmol per liter) and PE (0.133 mmol per liter). Both differences were significant. The L/P ratio was slightly lower in PE (8.42) than in H (9.24) and the controls (9.82). There were no significant differences among any of the groups.

The effects of sodium lactate infusion in the three groups of patients studied are given in Tables III to V and in Figs. 1 to 4. In normal pregnant women, blood lactate and pyruvate during the infusion averaged 193.59 and 141.2 per cent, respectively, above the

Table V. Effects of lactate infusion* in six pre-eclamptic patients

	Preinfusion	*Midinfusion*	*t*	*Per cent change*
Serum uric acid (mg./100 ml.)	7.08† ± 0.85	6.58† ± 1.12	t = 0.786 N.S.	92.73‡ ± 7.5
Uric acid clearance (C_{ur}) (ml./min.)	6.43 ± 1.61	1.20 ± 0.18	t = 7.205 <0.001	19.61 ± 5.49
Serum creatinine (mg./100 ml.)	0.75 ± 0.12	0.72 ± 0.12	t = 0.368 N.S.	96.3 ± 4.99
Creatinine clearance (C_{cr}) (ml./min.)	118.57 ± 8.96	135.26 ± 26.49	t = 1.335 N.S.	113.77 ± 18.17
Fractional uric acid clearance $\left(\frac{C_{ur}}{C_{cr}} \times 100\right)$	5.38 ± 1.04	0.92 ± 0.24	t = 9.35 <0.001	17.57 ± 5.09
Blood lactate (L) (mmol/L.)	1.067 ± 0.373	2.221 ± 0.479	t = 4.252 <0.01	219.83 ± 51.34
Blood pyruvate (P) (mmol/L.)	0.155 ± 0.073	0.209 ± 0.08	t = 1.127 N.S.	138.09 ± 30.91
L/P ratio	7.164 ± 1.374	11.655 ± 3.806	t = 2.482 <0.05	164.83 ± 55.74

*Intravenous infusion of 600 ml. of 1/6M sod. lactate over 50 minutes.
†Mean ± S.D.
‡Mean ± S.D. of the per cent of change over preinfusion values in each individual patient.

preinfusion levels. Serum creatinine and C_{cr} did not change. SUA was minimally elevated; 105.33 per cent of preinfusion values. C_{ur} and Fract. C_{ur} were significantly reduced as compared to preinfusion levels (21.53 and 23.18 per cent, respectively). The statistically significant differences between the pre- and midinfusion determinations were the increase in blood lactate and the reduction of C_{ur} and Fract. C_{ur} (Table III).

During the infusion in hypertensive pregnant women L averaged 175.22 per cent and P averaged 130.48 per cent of the preinfusion values. Serum creatinine remained the same, whereas C_{cr} was decreased slightly, i.e., 89.93 per cent of preinfusion measurement. SUA remained the same, whereas C_{ur} and Fract C_{ur} were decreased to 17.8 and 25.82 per cent of the preinfusion values, respectively. The only statistically significant differences between preinfusion and midinfusion determinations were the elevated L and P and the reduced C_{ur} and Fract. C_{ur} (Table IV).

In pre-eclamptic women, during the infusion, L averaged 219.83 per cent and P averaged 138.1 per cent of the baseline measurements. SUA was minimally decreased to 92.73 per cent of the preinfusion values. C_{ur} and Fract. C_{ur} were reduced to 19.61 and 17.57 per cent of the preinfusion values. Serum creatinine remained the same, whereas C_{cr} increased slightly to 113.77 per cent of the preinfusion values. The only statistically significant differences between the preinfusion and midinfusion determinations were the elevated L, the increased L/P ratio, and the reduced C_{ur} and Fract. C_{ur} (Table V).

After discontinuation of the infusion all determinations that showed a definite change tended to revert to the baseline values. This was not achieved in any of the three groups of patients for the time of observation (40 minutes) (Tables III to V). The only statistically significant differences between the postinfusion and baseline preinfusion determinations in all three groups were the still reduced C_{ur} and Fract. C_{ur}. Blood lactate was still statistically significantly higher in the normal and pre-eclamptic subjects but not in the hypertensive women. L/P ratio was significantly higher only in the normal pregnant women.

There were no statistically significant differences in the per cent change of SUA, C_{ur}, C_{cr}, or Fract. C_{ur} as a result of the lactate infusion or after its discontinuation among the three groups of patients. Correlation analysis was used to examine the relation between C_{ur} and both blood lactate and L/P ratios in all the patients studied. There was no correlation. The correlation coefficients were r = 0.193, P 0.173, and r = 0.22, P 0.111, respectively. Correlation analysis was then applied to each of the three groups of patients, i.e., normal, hypertensive, and pre-eclamptic, separately. Again, there were no correlations between C_{ur} and either blood lactate levels or L/P ratios. In normal pregnant women, the values were, r = 0.246, P 0.417, and r = 0.403, P 0.172, respectively. In hypertensive pregnant women the values were r = 0.317, P 0.161, and r = 0.209, P 0.362, respectively. In pre-eclamptic women the values were, r = − 0.185, P 0.474, and r = − 0.367, P 0.147. It has been shown that C_{ur} was universally decreased as a result of sodium lactate infusion and remained at lower values after infusion. We tried to correlate the degree of reduction of C_{ur} with the degree of increase in blood lactic acid levels in the three groups of patients. A negative correlation was

Postinfusion	*t*	*Per cent change*
6.918† ± 1.086	t = 0.255 N.S.	97.56‡ ± 6.07
1.862 ± 1.318	t = 4.906 <0.001	27.03 ± 11.36
0.708 ± 0.12	t = 0.482 N.S.	95.22 ± 7.62
14.369 ± 24.286	t = 0.363 N.S.	96.21 ± 16.87
1.555 ± 0.775	t = 6.591 <0.001	28.34 ± 10.48
1.708 ± 0.479	t = 2.362 <0.05	163.58 ± 19.33
0.183 ± 0.097	t = 0.52 N.S.	115.73 ± 37.14
10.944 ± 3.798	t = 2.093 N.S.	157.74 ± 65.93

demonstrated but it was not significant in any of the groups: r = − 0.242, P 0.5, r = − 0.111, P 0.6, and r = − 0.255, P 0.42, respectively.

Comment

Because posture affects RPF, GFR, sodium excretion, and uric acid excretion,[14] all of our patients were studied in the lateral recumbent position. The results of this study confirmed previous reports of hyperuricemia and impaired C_{ur} in PE.[1-5, 7] The reduced GFR in our pre-eclamptic patients concurred with previous studies.[8, 14] The blood lactate and pyruvate levels in our normal pregnant women were in the range reported.[15] Our findings of a lowered blood lactate, pyruvate, and L/P ratio in PE are in agreement with the study by Neumayer.[16] However, they disagree with other older reports of hyperlactacidemia[10, 11] in PE. The group of hypertensive pregnant women had higher SUA levels and impaired C_{ur} as compared to normal pregnant women. These findings are not uncommon in chronic hypertensive disease. The degree of change relative to normal pregnancy, however, was less marked than in pre-eclamptic women. In accord with previous studies the creatinine clearance was reduced in the hypertensive pregnant women.[14, 17]

Blood lactate was found to be elevated in chronic hypertensive disease. However, there are no previous reports of lactic and pyruvic acid levels in pregnant women with hypertension. Handler's study included four hypertensive women and, calculating from the figures reported, lactic acid was slightly higher in the hypertensive than the normal pregnant and pre-eclamptic women.[11] In this study of 22 hypertensive pregnant women blood lactic acid was lower, pyruvic acid was significantly lower, and L/P ratio lower in hypertensive than in normal pregnant women.

In agreement with previous reports,[7] C_{ur} is more impaired than C_{cr} in PE. This finding, expressed as a decreased Fract. C_{ur}, indicates that the decreased C_{ur} is not solely caused by a reduced GFR. This is expected from what we presently know about the mechanism of renal handling of uric acid.[18, 19] It is currently believed that plasma uric acid is filtered freely in the glomerulus and that 98 to 100 per cent of the filtered urate load is reabsorbed actively by the proximal tubule. The bulk of excreted uric acid is secreted by the tubules. Recent evidence indicates that postsecretory tubular reabsorption of urate occurs distal to or through the same site of secretion.[18, 19]

Recent studies showed a link between the volume of the extracellular fluid (ECF) and the tubular reabsorption of sodium and uric acid. Contraction of ECF volume caused by salt depletion and/or prolonged use of diuretics will markedly enhance proximal tubular reabsorption of sodium, urate, and possibly other ions.[20] Conversely, ECF volume expansion by glucose, mannitol, or hypertonic saline[21] will markedly enhance C_{ur}. In pregnant women, the relation between sodium excretion and C_{ur} is very strong. The supine recumbent position will produce striking antinatriuresis and simultaneous decrease in the Fract. C_{ur}.[22]

Tubular secretion of urate is probably directly related to plasma levels.[18] It is also affected by many drugs, for example, pyrazinamide, and metabolic products, particularly lactate.[9, 18] Lactate is present in high concentrations in the renal medulla, where it is generated by anaerobic metabolism. Studies of slices of renal tissue showed a steep corticomedullary gradient for both lactate[23] and urate.[24] This gradient is exaggerated under ischemic conditions or with the administration of certain diuretics known to inhibit uric acid excretion.[25] It is suggested that medullary lactate might interfere directly with tubular transport of uric acid.

Handler[11] suggested that the hyperuricemia of PE is due to excess lactic acid, produced by the hypoxic placenta, interfering with uric acid excretion. Our results do not agree with this theory. Blood lactic acid levels were actually lower in PE than in normal pregnancy. In fact, calculating from the figures given in his report, blood lactate levels in PE were not statistically different from those in normal controls, and the levels were slightly higher in the hypertensive women than both the pre-eclamptic and normal pregnant women. SUA was not found to correlate with blood lactate in PE.[10] Neither did we find correlation between blood lactate or L/P ratios with C_{ur} in any of

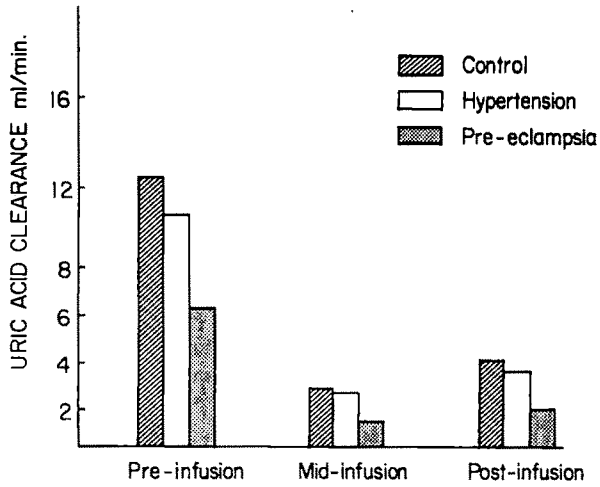


Fig. 1. Uric acid clearance in the three groups of patients in relation to sodium lactate infusion.

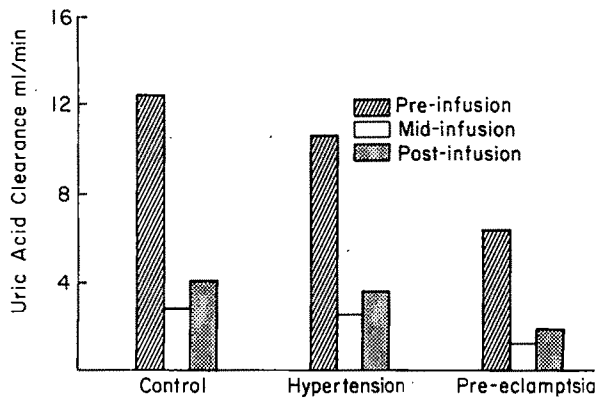


Fig. 2. The effect of lactate infusion on uric acid clearance in the three groups of patients studied.

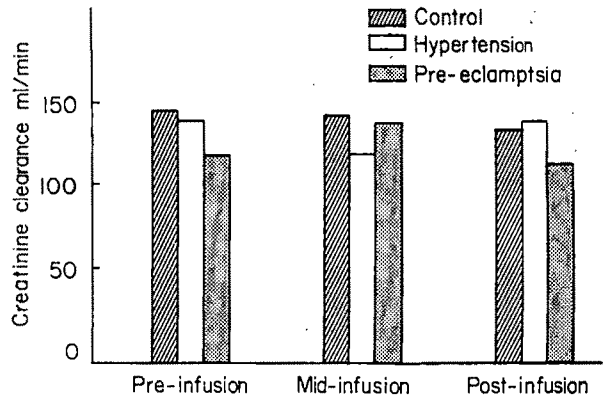


Fig. 3. Creatinine clearance in the three groups of patients in relation to sodium lactate infusion.

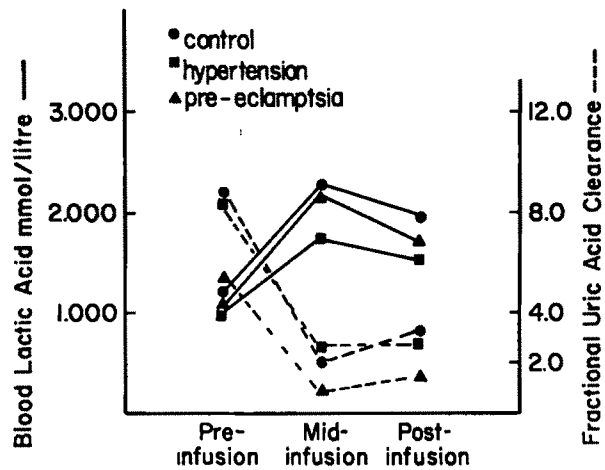


Fig. 4. Relation of blood lactic acid levels to fractional uric acid clearance in patients of the three groups who have been infused with sodium lactate.

the groups of patients studied or in the group as a whole. This is in contradistinction to Handler's finding of a significant negative correlation between blood lactate and C_{ur}/C_{cr} ratios in a group of normal, hypertensive, pre-eclamptic and eclamptic women. In the latter study, no attempt was made to separate the patients in groups. If the eclamptic patients were excluded, the correlation would have been less significant. Moreover, the correlation was made with C_{ur}/C_{cr} and not with C_{ur}.[11] This is not acceptable in the light of the present knowledge.

Sodium lactate infusion resulted in marked reduction of C_{ur} in all the patients. The degree of reduction was about the same as reported in nonpregnant subjects.[9] The degree of reduction was not different in the three groups of patients we studied. Neither was the rate or degree of recovery of the impaired C_{ur} after discontinuation of the infusion, different in the three groups. These findings demonstrate that while hyperlactacidemia induced by sodium lactate infusion causes reduction of C_{ur} in all pregnant women, blood lactic acid per se is not responsible for the reduced C_{ur} in PE.

There is evidence of a contracted plasma volume in PE.[26] Volume depletion is known to cause reduced C_{ur} and hyperuricemia. It has been shown that further depletion of ECF volume by sodium restriction and use of diuretics in a pre-eclamptic patient led to clinical deterioration and further increase in uric acid levels.[27]

Angiotension II (AII) has long been known to have profound renal effects. More recently it has been shown that AII infusion resulted in substantial immediate reduction in urate clearance.[28] The decrement of C_{ur} closely paralleled a fall in RPF. The reduced RPF caused a decrease of the available urate at the secretory sites. There is now evidence that renin secreted from the juxtaglomerular cells (JGC) forms AII locally, and the latter, acting on glomerular

arterioles, may influence the RBF and GFR. In addition, AII may regulate tubular function directly by acting on the tubular epithelial cells or indirectly through its hemodynamic effects.[29, 30] In a study comparing uric acid handling by the two kidneys in patients with unilateral renal artery stenosis, it was found that uric acid excretion per unit of GFR, by the ischemic kidney, was markedly less than by the other kidney.[31] In view of the above, this finding could possibly be ascribed to the local action of AII generated in the ischemic kidney. Similarly, in pre-eclampsia, the RPF is reduced[14, 17] and there is evidence of increased renin release by JGC. Increased number, swelling, degranulation, and exhaustion of the JGC have been noted in renal biopsy specimens from pre-eclamptic women.[32] Although it is difficult to tell whether these changes are causally related to the pathogenesis of PE or simply its result, the fact remains that the evidence cited can explain the reduced C_{ur} and the consequent hyperuricemia in this disease.

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Induction of labor with intravenous prostaglandin

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The present study utilizing an open label design evaluates the efficacy of prostaglandin $F_{2\alpha}$ in the induction of labor in normal and complicated primigravid and multigravid pregnancies and in particular in patients with an unripe cervix. The results reveal that labor was successfully induced in 33 of 38 (86.8 per cent) normal patients in the 0 to 5 Bishop group and in 17 of 18 (94.4 per cent) in the 6 to 13 Bishop group. In the complicated pregnancies (abnormal group) 26 to 28 (84 per cent) in the 0 to 5 Bishop group and 13 of 13 (100 per cent) in the 6 to 13 Bishop group were successfully induced. There were two cesarean sections for obstetric indications. Hypertonus occurred only four times and responded to dose reduction. The most common problem—nausea and vomiting (29 per cent)—was easily controlled. Prostaglandin when judiciously used appears to be a safe drug for the induction of labor at term in normal as well as complicated pregnancies and in patients with low inducibility scores.

THE NOTABLE accomplishment of Bergstrom and associates[1] in characterizing the exact structure of two prostaglandins was soon followed by the development of a biosynthetic method able to achieve production of commercial quantities of prostaglandins available heretofore only in small quantities at great cost.

Prostaglandin is, in fact, not a new compound and initial observations of its effect were first reported in 1930 by Kurzrok and Lieb[2] of New York and later by Goldblatt[3] in England and von Euler[4, 5] in Sweden, the latter having misnamed it, thinking that the pharmacologic activity of the seminal extracts utilized in his experiments was derived from the prostate gland. Much has been written on the subject since then and several excellent review articles on its role in reproductive physiology are available to the reader.[6–9]

It was the action of prostaglandin on human myometrium which ultimately led to its exploration in the induction of labor.[10]

In the past few years several papers have appeared reporting the therapeutic value of intravenous prostaglandin $F_{2\alpha}$ in inducing labor at term.[11–16]

The more recent studies [14–16] attempted to objectively evaluate the inducibility status of the patient by utilizing the pelvic score described by Bishop[17] and there is thus some basis for comparison of results. These studies were double blind and compared prostaglandin to oxytocin. Most of the patients had uncomplicated pregnancies and were in the inducible category.

These studies as well as several others utilizing small numbers of patients had alluded to the efficacy of prostaglandin $F_{2\alpha}$ in the preterm or difficult to induce cervix.[18–23]

It was the purpose of this study to evaluate, in an open label design, prostaglandin $F_{2\alpha}$ in the induction of labor in normal and complicated primigravid and multigravid pregnancies and, in particular, in patients with an unripe cervix.

Materials and method

Patients. Patients were selected from volunteer gravid women in weeks 30 to 44 of pregnancy. The group included complicated pregnancies, i.e., diabetes, Rh sensitization, premature rupture of membranes, post datism, and toxemia, as well as normal, elective inductions at term with low Bishop scores.

Patients were selected from the private as well as the service sector.

Selection criteria. One hundred (100) volunteer women were selected for this study. Selection criteria

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Table I. Dose schedule: PGF_2, 50 μg per cubic centimeter

Harvard infusion pump flow selector Nos.	*Flow rate (c.c./min.)*	*Drug dosage (μg/min.)*	*Duration of infusion (hr.)*
5	0.05	2.5	0.5
7	0.10	5.0	0.5
9	0.20	10.0	1.0
11	0.40	20.0	1.0
13	0.80	40.0	2.+
			As needed

Table II. Other major diagnoses (abnormal)

	Bishop score 0-5		*Bishop score 6-13*	
Diagnosis	*No. of cases*	*Per cent of patients*	*No. of cases*	*Per cent of patients*
Excessive weight gain	6	19.4	0	0
Diabetes mellitus	1	3.2	0	0
Post datism	13	41.9	7	53.8
Renal hypertension	1	3.2	0	0
Rh incompatibility	2	6.5	1	7.7
Toxemia of pregnancy	9	29.0	1	7.7
Premature rupture	6	19.4	5	38.5
No. of patients	31	100	13	100

*Several patients had multiple diagnoses.

for patient entry into the study were (1) gestational age 30 to 43 weeks, (2) induction indicated or elective, (3) age 16 to 40 years, (4) weight 90 to 230 pounds, and (5) live fetus.

Specific exclusions. Patients excluded were (1) those with 6 or more term pregnancies, (2) those in true labor at time of admission, (3) those with previous cesarean births or hysterotomies, (4) those in whom major degrees of fetalopelvic disproportion might have been present, and (5) those in whom there was clinical suspicion or definite evidence of pre-existing fetal distress.

Supplies. Supplies included prostaglandin, 50 μg per cubic centimeter, derived by mixing a 1.5 c.c. vial containing 7.5 mg. of prostaglandin $F_{2\alpha}$, with sterile 5 per cent dextrose in water to a total volume of 150 c.c.

Procedure. On admission to the study, the following procedure was followed. (1) Informed consent was obtained in all cases in conformity with regulations of HEW, 1973. (2) Baseline measurements, i.e., maternal vital signs and fetal heart rate, were recorded. Chemistries, CBC, and urinalysis were obtained prior to induction and repeated 12 hours post partum. (3) Patient history was obtained. (4) All patients were evaluated 24 hours prior to and on admission. Bishop scores were based on two or three independent observations and the highest Bishop score was assigned to the patient. (5) After the usual preparation, a 5 per cent infusion of intravenous glucose was started. Monitoring the patient with a Corometrics Fetal Monitor was carried out for 30 minutes prior to administration of prostaglandin $F_{2\alpha}$.

Dosage and rates of administration. Prostaglandin was intravenously given in graded increments in accordance with a predetermined dosage schedule via a Harvard Pump (see Table I).

When labor of good quality (as manifested by progressive dilation and effacement of the cervix) was induced and maintained at any dosage level, the infusion was continued at this rate. If induction was not progressing satisfactorily in our judgment at any dose level, then the dose was augmented as per schedule. If, at the end of 10 hours, labor was not satisfactorily induced, treatment was stopped and appropriate therapy instituted to effect delivery of a healthy infant.

Observations. All observations were recorded on the proper computer forms.

Vital signs. Vital signs were obtained and recorded at 30 minute intervals. This regimen was continued until either (1) the subject had delivered or (2) the subject had been graded a failure for delivery of the fetus.

Fetal monitoring was continued throughout the time of infusion. A trained, on-duty nurse was assigned to the patient to continuously observe uterine contrac-

Table III. Summary of results

	Normal		*Abnormal*	
	Bishop score 0-5	*Bishop score 6-13*	*Bishop score 0-5*	*Bishop score 6-13*
No. of subjects	38	18	31	13
No. induced	33 (87%)	17 (94%)	28 (90%)	13 (100%)
No. delivered	32 (84%)	17 (94%)	26 (84%)	13 (100%)
No. of cesarean sections	0	0	2 (6.5%)	0
Ave. time to labor induction (min.)	133	133	188	136
Ave. time labor induction to delivery	218	157	233	302
Ave. time to delivery	351	290	421	338
Ave. Apgar score at delivery	8.5	8.7	8.6	8.9
Ave. Apgar score 5 min. after delivery	9.5	9.8	9.4	9.8
Ave. total dose at induction (mg.)	1.37	1.42	2.42	1.20
Ave. total dose at delivery (mg.)	6.13	5.48	7.23	6.41

Table IV. Labor induction: Success ratio and time from start of medication infusion

		Success				*Time (min.)*			
Class	*Bishop score group*	*No.*	*Success*	*Fail*	*Per cent Success*	*No.*	*Mean*	*S.E.M.*	*Range*
Normal	0-5	38	33	5	86.8	33	133	10	30-240
	6-13	18	17	1	94.4	16	133	17	30-300
Abnormal	0-5	31	28	3	90.3	27	188	23	45-630
	6-13	13	13	0	100.0	13	136	15	60-250

tions and fetal heart rate patterns as well as the gravid mother's response and well being. These observations were performed in collaboration with the authors, who undertook continuous responsibility for each study patient.

In no instance were membranes artificially ruptured prior to the onset of active labor. Labor was defined by the accepted criteria of progress in dilatation and effacement accompanied by regular and adequate uterine contraction patterns.

Contraction intervals were carefully observed for evidence of impending hypertonus. When contractions occurred at a frequency greater than four to five for each 10 minute period, the dose was diminished.

Upon delivery, all fetuses were evaluated by Apgar score and observed in our nurseries for any sequelae.

Mothers were evaluated specifically at 1 hour and 12 hours post partum, according to our protocol, for any complications referable to the drug.

Results

The report concerns 100 patients and they are separated into normal and abnormal groups. Abnormal patients were those who had one or more major diagnosis complicating their pregnancies, as listed in Table II.

The results were also tabulated separately in two Bishop score groups 0 to 5 "difficult"; 6-13, "inducible").

The most common complications, calculated as per cent of abnormal patients, were excessive weight gain (six of 44 patients = 14 per cent), postdatism (20 of 44 patients = 45 per cent), toxemia of pregnancy (10 of 44 patients = 23 per cent), and premature rupture of the membranes (11 of 44 patients = 25 per cent).

A summary of all data in several major areas is given in Table III, and a more detailed description follows.

Labor (Tables IV through VIII). Labor was successfully induced in 33 of 38 (86.8 per cent) normal

Table V. Delivery: Success rate and time

Class	Bishop score group	Success ratio				Time (min.)			
		No.	Success	Fail*	Per cent Success	No.	Mean	S.E.M.	Range
Normal	0-5	38	32	6	84.2	32	351	25	133-674
	6-13	18	17	1	94.4	17	290	32	140-685
Abnormal	0-5	31	26	5	83.9	26	421	37	149-901
	6-13	13	13	0	100.0	13	339	49	169-675

*Cesarean sections included as failures.

Table VI. Time in minutes from labor induction to delivery

Class	Bishop score 0-5				Bishop score 6-13			
	No.	Mean	S.E.M.	Range	No.	Mean	S.E.M.	Range
Normal	32	218	23	43-554	17	166	24	20-385
Abnormal	26	233	30	45-660	13	203	41	22-465

Table VII. Total dose to labor induction (in milligrams)

Class	Bishop score 0-5				Bishop score 6-13			
	No.	Mean	S.E.M.	Range	No.	Mean	S.E.M.	Range
Normal	33	1.37	0.20	0.08-4.42	17	1.42	0.45	0.08-6.82
Abnormal	28	2.42	0.49	0.15-8.91	13	1.20	0.25	0.22-3.22

Table VIII. Total dose to delivery (in milligrams)

Class	Bishop score 0-5				Bishop score 6-13			
	No.	Mean	S.E.M.	Range	No.	Mean	S.E.M.	Range
Normal	32	6.13	0.77	0.82-19.4	17	5.48	1.37	0.82-22.4
Abnormal	26	7.23	0.94	0.68-19.9	13	6.41	1.73	1.42-21.2

patients in the 0 to 5 Bishop group and in 17 of 18 (94.4 per cent) patients in the 6 to 13 Bishop group. In one patient labor was initiated but delivery did not occur within the acceptable time interval and, though tabulated as a success in Table IV, it is appropriately listed as a delivery failure in Table V.

The mean time interval from start of medication to initiation of labor (latent phase) was 133 minutes for both Bishop groups and the ranges were 30 to 240 and 30 to 300 minutes (Table IV).

The abnormal group had a 28 of 31 or 90.3 per cent successful induction rate in the 0 to 5 score group and 100 per cent or 13 of 13 in the 6 to 13 Bishop group. There were two patients who failed to deliver but who were in active labor and were sectioned for cephalopelvic disproportion. In three, patients labor could not be initiated. This is shown in Table V as delivery success ratio 26/31 or 83.9 per cent.

The mean time interval from medication to labor in the abnormal group was 188 minutes for patients whose Bishop score ranged from 0 to 5 and 136 minutes for the 6 to 13 group. Their ranges were 45 to 630 and 60 to 250 minutes, respectively (Table IV).

The total time from start of medication to delivery is depicted in Table V for the different groups.

The time from labor to delivery is noted in Table V.

Thus we see that the mean duration of labor in normal patients with Bishop score 0 to 5 was 218 minutes (range 43 to 554 minutes) and 166 minutes in the Bishop group 6 to 13 (range 20 to 385 minutes). The mean duration of labor in the abnormal patients was 233 minutes (range 22 to 465 minutes) in the 6 to 13 Bishop group.

The total drug dose to labor induction was 1.37 and 1.42 mg. for the normal patients in the 0 to 5 and 6 to 13 Bishop groups. In the abnormal patients it was 1.42

Table IX. Mean fetal Apgar scores

Group	*No.*	*Mean*	*S.E.M.*	*Range*
Normal:				
Bishop score 0-5				
At delivery	32	8.5	0.21	5-10
5 min. after delivery	32	9.5	0.14	7-10
Bishop score 6-13				
At delivery	17	8.7	0.16	7-9
5 min. after delivery	17	9.8	0.09	9-10
Abnormal:				
Bishop score 0-5				
At delivery	26	8.6	0.24	3-9
5 min. after delivery	26	9.4	0.17	6-10
Bishop score 6-13				
At delivery	13	8.9	0.08	8-9
5 min. after delivery	13	9.8	0.11	9-10

and 2.20 mg. in the 0 to 5 and 6 to 13 Bishop groups (Table VII).

The total drug dose to delivery was 6.13 and 5.48 mg. for the 0 to 5 and 6 to 13 Bishop groups in normal patients and 7.23 and 6.41 mg. for the 0 to 5 and 6 to 13 Bishop groups in abnormal patients (Table VIII).

The average maximum rate of infusion was 0.603 c.c. per minute or 30 μg per minute.

Fetus. Fetal safety, as always, is paramount and one must remain severely critical when evaluating a drug that interferes with a naturally occurring process. Regard for the safety of the fetus by precise monitoring becomes of even greater and more particular concern when one considers that many of our patients were induced with unengaged vertices and with low Bishop scores (average Bishop score 4.76).

Table IX reveals the mean fetal Apgar scores. The 1 minute Apgar score average was 8.65 and the 5 minute average was 9.65. This would tend to demonstrate by present-day parameters a high degree of fetal safety. No infant complications developed during their 4 to 5 day hospital stay which could implicate prostaglandin.

Adverse reactions. The incidence of adverse reactions in the normal and abnormal patients is seen in Table X.

The most common problem, nausea and vomiting, appeared with equal frequency in both groups and was easily controlled by 25 mg. of promethazine hydrochloride. Nausea and vomiting occurred in 20 per cent (29 patients).

Hypertonus. Uterine hypertonicity was seen in only three patients, one of whom demonstrated tetanic contractions. These were reversed by discontinuation of the drug, turning the patient on her left side, and

Table X. Adverse reactions

	Bishop score 0-5, No./patient		*Bishop score 6-13, No./patient*	
Type of adverse reaction	*No.*	*%*	*No.*	*%*
Normal:				
Phlebitis			1	5.8
Nausea	1	2.6		
Nausea and vomiting	3	7.9		
Vomiting	14	36.8	2	11.1
Diarrhea	2	5.3	1	5.6
Tetanic contraction	1	2.6		
Fetal heart rate, variable decelerations	4	10.5		
Number of patients with one or more adverse reactions reported	19	50.0	3	16.7
Number of patients with no adverse reactions reported	19	50.0	15	83.3
Number of patients	38	100.0	18	100.0
Abnormal:				
Nausea and vomiting	1	3.2	1	7.7
Vomiting	7	22.6	6	46.2
Diarrhea			1	7.7
Uterine hypertonicity	2	6.5		
Hysteria	1	3.2		
Number of patients with one or more adverse reactions reported	10	32.3	6	46.2
Number of patients with no adverse reactions reported	21	67.7	7	53.8
Number of patients	31	100.0	13	100.0

administering oxygen. The Apgar scores of these three fetuses were above 8 and 9, respectively.

Unsuccessful inductions. Twelve patients failed to deliver. One patient came to cesarean section for cephalopelvic disproportion after full dilatation with failure to descend. One patient had a cesarean hysterectomy because the membranes had been ruptured for more than 24 hours and she had requested sterilization.

Ten patients delivered vaginally within 1 to 7 days after cessation of prostaglandin infusion.

Vital signs and laboratory data. There were no significant differences in vital signs at the 1 and 12 hour postdelivery intervals.

The pre- and postinfusion hemoglobin and hematocrit did not reveal any significant differences.

Comment

The initial reports by Karim and associates[11, 12] in 1968 and 1969 established the effectiveness of intravenous prostaglandin in the induction of labor at term.

In 1971, in a double-blind preliminary study, Anderson and associates[18] went one step further by an objective attempt at determining the inducibility of

their patients with the Bishop[17] pelvic scoring system.

Their subsequent papers and those of others,[14–16, 18–20] utilizing the same protocol design, allowed for a comparison of results.

These studies reported efficacy results that were very nearly similar and that prostaglandin was not a more effective oxytocic in term labor induction than Pitocin or Syntocinon.

Several papers at this time[7] appeared which alluded to the efficacy of prostaglandin $F_{2\alpha}$ in the preterm cervix or the difficult to induce cervix.

Barden[22] evaluated 10 patients with premature rupture of the membranes prior to term with an average Bishop score of 5.6. Starting at a dosage level of 2.5 μg per minute, which was doubled at 60 minute intervals until labor was established, or up to a maximum dosage level of 20 μg per minute, he noted only occasional instances of hypertonus with no fetal or maternal morbidity attributable to the drug. Eight of these patients delivered vaginally, two by cesarean section.

In a preliminary report by Tchilinguirian[23] 100 per cent, i.e., seven of seven high-risk patients, delivered vaginally, two with Bishop scores 0 to 4, three with 5 to 7, and two in the 8 to 10 range. The dosage levels were from 2.5 to 40 μg per minute. With regard to hypertonus, some transient episodes of tachysystole and some elevation of baseline uterine tone were noted, but no fetal distress was detected.

Elias[24] reported on 16 prostaglandin $F_{2\alpha}$ inductions with the following indications: 7, pre-eclampsia; 6, postmature; 1, gestational diabetes; 1, previous antepartum hemorrhage; 1, rhesus factor. These were high-risk patients with low Bishop scores, i.e., three with a score of 2, two patients with 3, five with 4, two with 5, three with 6, and only one patient with a high score of 9. Labor was successfully induced in all cases. The maximum infusion rate was between 5 and 10 μg per minute. There were no maternal or fetal complications attributable to prostaglandin.

These reports led us to believe that the unfavorable cervix, in the high-risk as well as in elective candidates, would respond to prostaglandin $F_{2\alpha}$

In the evaluation of prostaglandin $F_{2\alpha}$ therefore, we attempted to answer the following questions: (1) Is prostaglandin efficacious in the low Bishop score patient? (2) Could it be used safely in the high-risk as well as elective case? (3) Is hypertonus a real problem associated with the use of prostaglandin $F_{2\alpha}$?

The results of our study, which reveal an over-all successful induction rate of 88 per cent and 84 per cent successful induction rate in the 0 to 5 Bishop category, indicate the value of prostaglandin in low inducibility score patients.

Vakhariya and Sherman[15] reported a 94 per cent successful induction rate with prostaglandin $F_{2\alpha}$ with a lower induction delivery time in the difficult cases. Though this was not statistically significant vs. Pitocin in their comparative study, they did allude to its potential greater effectiveness in difficult situations. Anderson and associates[14] in their comparative study, recorded a success rate of 85 per cent for oxytocin, 76 per cent for prostaglandin $F_{2\alpha}$ and 83 per cent for prostaglandin E_2. They had more low Bishop score patients in their prostaglandin $F_{2\alpha}$ group. The mean infusion delivery interval was shorter in the prostaglandin $F_{2\alpha}$ patients by 1.4 hours in the 0 to 6 Bishop category, and by 1.25 hours in the 7 to 13 Bishop group. This shorter interval, they concluded, may be the advantage of prostaglandin $F_{2\alpha}$ over Pitocin.

Spellacy and associates,[16] in a recent paper, found an over-all success of 74.5 per cent for the prostaglandin $F_{2\alpha}$ group and 66.4 per cent success rate for the oxytocin group, a difference which was calculated not to be significant. They also found no significant difference in the latent phase nor in the mean duration of labor between the two groups. It was also noted that with similar Bishop scores there was no difference in efficacy between prostaglandin and oxytocin.

With regard to maternal safety there seems little doubt that, judiciously used, the drug is safe.

The high-risk patients in our study group fared as well as the normal patients and maternal and fetal safety has been well documented by our results.

Hypertonus appears to be the problem at large and point of controversy.

Spellacy and associates[16] concluded that the drug provoked an inordinate degree. They defined hypertonus as "basal amniotic fluid pressure greater than 15 mm. Hg measured directly or the palpation of abnormally hard and frequent contractions if the patient was not being internally monitored."

Spellacy's paper reports nine cesarean sections in 115 prostaglandin patients, none in the oxytocin group. All nine sections were done for fetal distress (bradycardia). Hypertonus was seen in six cases and one infant (35449) died from respiratory distress at 18 hours of age.[16]

Anderson's group[14] described hypertonus as "baseline intrauterine pressure greater than 15 mm. Hg or tachysystole (frequency of contractions greater than two per minute)." Seven of their patients developed transient periods of hypertonus at various infusion rates. The problem was corrected on discontinuation of the drug infusion and there were no associated neonatal problems. The cesarean section rate was 1 per cent after a synthetic oxytocin failure, the indication being cephalopelvic disproportion. They

concluded, with regard to uterine hypertonus, that the uterus does seem to be more sensitive to alterations in dosage rates of prostaglandin $F_{2\alpha}$ than to oxytocin, but careful adjustment of prostaglandin $F_{2\alpha}$ dosage had essentially eliminated the problem, as they had no episodes of hypertonus or tachysystole in their last 40 cases.

Vakhariya and Sherman[15] reported nine cases of hypertonus, two of which were iatrogenic (accidental injection of a large bolus of the drug when a kink in the intravenous tube was released). They concluded that prostaglandin $F_{2\alpha}$ seems to be as efficacious and as safe as Pitocin for the induction of labor in multiparas at term.

We defined hypertonus as a baseline pressure greater than 15 mm. Hg or a change in baseline pressure greater than 10 mm. Hg and a frequency of contractions greater than five in any 10 minute period.

We did not have any significant elevations in baseline pressure and only four cases of hypertonus and one case with a tetanic contraction. All delivered vaginally and there were no neonatal problems.

It appeared to us that the low incidence of hypertonus was the result of our built-in safeguard of reducing the dosage level when contractions reached five per minute.

The results reported in this paper and the investigators cited above are at variance with the report by Spellacy. While one must heed his cautious conclusions, from our own observations and work, which resulted in the successful induction of 88 of 100 patients with an average Bishop score of 4.76 and 1 minute and 5 minute Apgar scores of 8.65 and 9.65, respectively, it can only be concluded that prostaglandin $F_{2\alpha}$ when used judiciously, guided by continuous fetal monitoring, is safe and efficacious for the induction of labor in the unripe cervix.

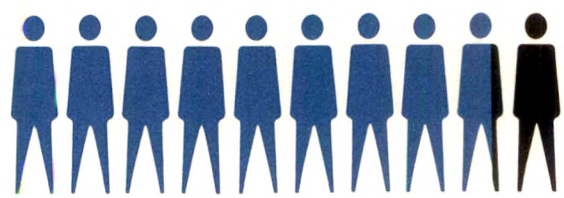
The authors wish to express their thanks to The Upjohn Company for their cooperation, particularly to Ed Kirk and Lou Piccoli for their help in the project. We also wish to thank Dr. M. Leon Tancer, Director of Obstetrics and Gynecology at The Brookdale Hospital Medical Center, for his review of the manuscript and his encouragement throughout the project.

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Some straight talk about acute cystitis therapy.

There's been a lot of discussion about what constitutes the best therapy for acute cystitis. Issues are being raised about resistance, fecal flora, spectrum of activity. But the important issues are still efficacy, safety and economy. Gantrisin® (sulfisoxazole) offers a superior balance of these three basic needs in acute cystitis.[1-4]* Now, a new study confirms Gantrisin efficacy. In this study, as often occurs in medical practice, therapy was initiated at the same time cultures were taken. The results of this study corroborate one fact. When you suspect gram-negative organisms† while awaiting culture results, you can prescribe Gantrisin with confidence. The results? 89% of 251 patients studied achieved sterile urine. A straight 89%.



*nonobstructed; due to susceptible organisms.

†Susceptible strains of *E. coli, Klebsiella-Aerobacter, P. vulgaris, P. mirabilis* and also gram-positive *Staph. aureus.*

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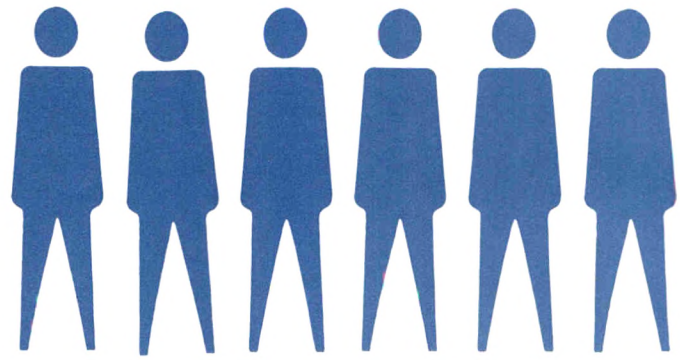
Please see summary of product information on the last page of this advertisement.

ROCHE

Straight talk about Gantrisin® in acute cystitis*

sulfisoxazole/Roche

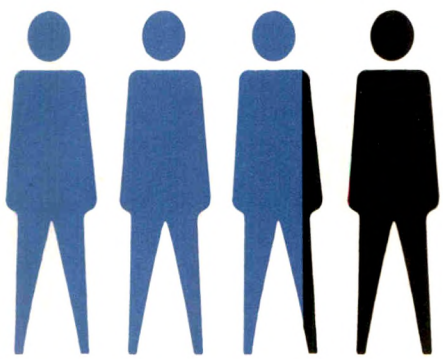
In a new study of Gantrisin (sulfisoxazole) in acute lower urinary tract infections, 89% of patients achieved sterile urine.†



No. of patients	Sterile urine	Clear culture (1000 or less organisms/ml urine)	Clear culture (10,000 or less organisms/ml urine)
251	89% (224)	90% (226)	92% (232)

Over the years Gantrisin (sulfisoxazole) has been the subject of continuing clinical research. There are many references which attest to its high degree of efficac in acute cystitis. Now a new clinical study of acute lowe urinary tract infection again demonstrates Gantrisin effectiveness. The pathogens causing these infections were *E. coli, Klebsiella-Aerobacter, P. vulgaris* and *P. mirabilis*, and the results—Gantrisin achieved 89% effectiveness.

*nonobstructed; due to susceptible organisms
†Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110



Gantrisin (sulfisoxazole) offers an established record of safety

Gantrisin introduced a new era of sulfonamide therapy coupling effectiveness and relative safety.[1-3] Side effects are few. In this study only 2% of the patients experienced side effects, which were mild. These included drowsiness, fatigue, rash, pruritus, diarrhea, nausea, vomiting, headache. The high solubility of Gantrisin minimizes risk of crystalluria and renal damage. However, as with any sulfonamide therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination.

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3. Stamey TA: *Urinary Infections*. Baltimore, The Williams and Wilkins Co., 1972, pp. 280-282

Gantrisin (sulfisoxazole) costs less than most therapies

• Few antibacterials can approach the economy of Gantrisin therapy. The average cost of 10-day Gantrisin therapy is less than 10 days of most other antibacterials.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Nonobstructed urinary tract infections (mainly cystitis, pyelitis, pyelonephritis) due to susceptible organisms.

IMPORTANT NOTE: *In vitro* sensitivity tests not always reliable; must be coordinated with bacteriological and clinical response. Add aminobenzoic acid to follow-up culture media. Increasing frequency of resistant organisms limits usefulness of antibacterial agents, especially in chronic and recurrent urinary infections. Maximum safe total sulfonamide blood levels, 20 mg/100 ml; measure levels as variations may occur.

Contraindications: Hypersensitivity to sulfonamides; infants less than 2 months of age; pregnancy at term and during the nursing period.

Warnings: Safety in pregnancy not established. Do not use for Group A beta-hemolytic streptococcal infections, as sequelae (rheumatic fever, glomerulonephritis) are not prevented. Deaths reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. CBC and urinalysis with careful microscopic examination should be performed frequently.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy or bronchial asthma. Hemolysis, frequently dose-related, may occur in glucose-6-phosphate dehydrogenase-deficient patients. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia; *Allergic reactions:* Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis; *Gastrointestinal reactions:* Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis; *C.N.S. reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia; *Miscellaneous reactions:* Drug fever, chills and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred. Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Contraindicated in infants under 2 months except in the treatment of congenital toxoplasmosis as adjunctive therapy with pyrimethamine.

Usual adult dosage—2 to 4 Gm initially, then 4 to 8 Gm/24 hrs in 4 to 6 doses. *Usual dosage for infants over 2 months and children*—½ 24-hrs dose initially, then 150 mg/kg/24 hrs in 4 to 6 doses; not over 6 Gm/24 hrs.

How Supplied: Tablets containing 0.5 Gm sulfisoxazole, white, scored—bottles of 100, 500 and 1000; drums of 5000; Tel-E-Dose® packages of 100; Prescription Paks of 100, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Gantrisin®

sulfisoxazole/Roche

4 to 8 tablets (0.5 Gm each) *stat*, 2 to 4 tablets *q.i.d.*

A superior balance of efficacy, safety and economy in acute cystitis therapy

Articles to appear in early issues

Fluctuations of fetal hemoglobin in sickle-cell anemia
J. C. Morrison, M.D., F.A.C.O.G., W. D. Whybrew, M.S., E. T. Bucovaz, Ph.D., and W. L. Wiser, M.D., F.A.C.O.G.
Memphis, Tennessee

Venous distensibility during pregnancy determined by graded venous congestion
B. Norman Barwin, M.D., and I. C. Roddie, M.D.
Ottawa, Ontario, Canada

Bacterial growth inhibition by amniotic fluid. VI. Evidence for a zinc-peptide antibacterial system
Patrick Schlievert, B.S., William Johnson, Ph.D., and Rudolph P. Galask, M.D., M.S.
Iowa City, Iowa

Suboptimal pregnancy outcome among women with prior abortions and premature births
Steve J. Funderburk, M.D., Donald Guthrie, Ph.D., and David Meldrum, M.D.
Los Angeles, California

The response of the human Fallopian tube to ergonovine and methyl-ergonovine in vivo
Elsimar M. Coutinho, M.D., Hugo Maia, M.D., and Lusia Nascimento, M.D.
Salvador, Bahia, Brazil

Identification of cold-insoluble globulin in amniotic fluid
Anthony B. Chen, Ph.D., Michael W. Mosesson, M.D., and George I. Solish, M.D.
Brooklyn, New York

Differential ovarian and adrenal vein catheterization
Anne Colston Wentz, M.D., Robert I. White, Jr., M.D., Claude J. Migeon, M.D., Tah Hsiung Hsu, M.D., H. Verdain Barnes, M.D., and Georgeanna Seegar Jones, M.D.
Baltimore, Maryland

Diagnostic laparoscopy: A prognostic aid in the surgical management of infertility
Robert Israel, M.D., and Charles M. March, M.D.
Los Angeles, California

Endocrine-metabolic response to acute starvation in human gestation
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Mead Johnson announces

OVCON®

one name to remember
in low-dose oral contraceptives

two doses
from which to select

LOW DOSE

LOWER DOSE

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

OVCON®-35*

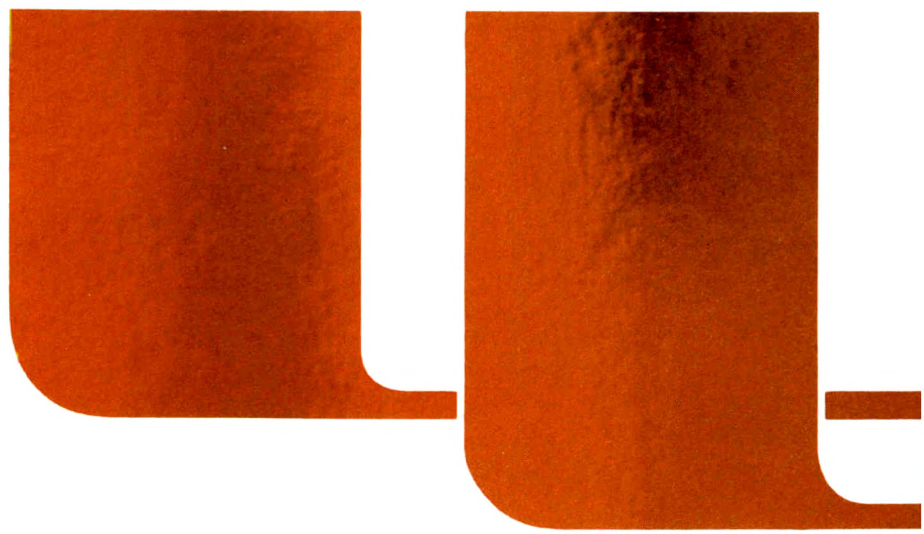
21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

For Brief Summary, please see last page of this advertisement.

One name to remember in combination oral contraceptive effectiveness...

OVCON®

two doses from which to select



providing...

- **effective low-dose contraceptive protection***
- **low incidence of common side effects†**
- **acceptable cycle control†**
- **in-depth clinical studies in widely different populations**

Mead Johnson LABORATORIES

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

tested in 1,028 women for 9,558 cycles[1]

Although these women represented a wide range of socioeconomic groups with inherent differences in motivation, pregnancy rate (Pearl's formula) was 0.13 pregnancies per 100 woman years due to method failure and 0.75 pregnancies per 100 woman years due to patient failure. This results in a use-effectiveness of 0.88 pregnancies per 100 woman years.

Few women—2.7%—discontinued therapy for cycle-related reasons . . . and these were not necessarily spotting or breakthrough bleeding, but included amenorrhea and what women considered bleeding too little or too much. There was a discontinuation rate of 10.8% for all other on-therapy conditions, which, however, were not necessarily caused by Ovcon-50.

OVCON®-35*

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

tested in 1,861 women for 20,230 cycles[1]

In these women, with a wide range of backgrounds and motivations, there was effective control of conception. Pregnancy rate (Pearl's formula) due to method failure was 0.41 pregnancies per 100 woman years, and 0.95 pregnancies per 100 woman years were due to patient failure. This results in a use-effectiveness of 1.36 pregnancies per 100 woman years.

There was a higher discontinuation rate —11.6%—for cycle-related reasons with Ovcon-35 than with Ovcon-50, but, again, reasons included any spotting as well as amenorrhea and bleeding too much, too little, or irregularly. On the other hand, the discontinuation rate for all other on-therapy conditions, which were not necessarily related to Ovcon-35, was quite low—7.1%.

1. Data on file, Mead Johnson Laboratories.

OVCON-50 and OVCON-35* offer the advantages of effective low-dose protection and of uninterrupted regimens— 21 active tablets and 7 inert tablets

For Brief Summary, please see following page.

*The effectiveness of Ovcon-35 is somewhat lower than higher-dose combination products.

†See "Special Note" section of prescribing information on last page of this advertisement.

two dosages from which to select

LOW DOSE
OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets.

LOWER DOSE
OVCON®-35

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. The effectiveness of OVCON-35 is somewhat lower than higher-dose combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons due to menstrual disorders and irregularities appears to be higher for OVCON-35 than that observed with higher-dose combination products. An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Oral contraception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen dependent neoplasia; undiagnosed abnormal genital bleeding; known or suspected pregnancy.

Warnings: If signs of thrombotic and thromboembolic disorders (thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis) occur or are suspected, use of the drug should be discontinued immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug use was discontinued and not enhanced by long-term use.[1-10]) If gradual or sudden, partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11-13] Safety of use in pregnancy has not been established, therefore pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant cannot be determined at this time. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in short-term as well as long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

Precautions: A thorough history and physical examination of breasts and pelvic organs should include Papanicolaou smears. (Estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after the drug has been withdrawn for two months. Under the influence of these drugs, pre-existing uterine fibromyomata may increase in size. Some conditions (epilepsy, migraine, asthma, cardiac or renal dysfunction) might be influenced by fluid retention. Observe carefully for such. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged OVCON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. Diabetic patients should be carefully observed while receiving such therapy. The age of the patient constitutes no absolute limiting factor, although these drugs may mask the onset of the climacteric. The pathologist should be advised of OVCON therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. If cholestatic jaundice occurs, OVCON should be discontinued. This condition is more likely to occur in patients with a history of cholestatic jaundice of pregnancy.

Adverse Reactions Observed in Patients Receiving Oral Contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage and gall bladder disease. Suggestive evidence, neither confirmed nor refuted, between use and: neuro-ocular lesions (retinal thrombosis and optic neuritis) and hepatic lesions with or without intra-abdominal bleeding. Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps and bloating), breakthrough bleeding, change in menstrual flow, spotting, amenorrhea during and after treatment, breast changes (tenderness, enlargement and secretion), mental depression, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals, edema, chloasma or melasma (which may persist), cholestatic jaundice, migraine, rash (allergic). Reported association with use, neither confirmed nor refuted: anovulation post treatment; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; intolerance to contact lenses; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; vaginitis. *May Alter Laboratory Results in:* Hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X, decrease in anti-thrombin III and an increase in norepinephrine-induced platelet aggregability), thyroid function (increase in PBI, and butanol extractable protein bound iodine and decrease in T_3 uptake values), metyrapone test, pregnanediol determination.

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FETUS, PLACENTA, AND NEWBORN

The mechanical properties of prematurely and non–prematurely ruptured membranes

Methods and preliminary results

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The mechanical properties of the chorioamniotic membranes have been studied by several investigators over the past 100 years. No relationship between membrane strength, as measured by rupture tension, and premature or non–premature rupture of the membranes has been demonstrable. In the present study, several measures of the mechanical properties of the chorioamniotic membranes were examined. These included thickness, rupture tension, work to rupture, strain to rupture, and moduli of elasticity (Young). Prematurely and non–prematurely ruptured membranes differed with respect to thickness near the rupture site and Young's modulus near the placenta. Differences between the groups for the other parameters were not significant. This study suggests that there may be inherent differences between membranes which rupture prematurely and those which do not.

PREMATURE labor is often associated with premature rupture of the membranes (PROM) and represents a significant clinical problem by contributing to perinatal morbidity and death. The etiology of PROM, however, remains unclear.

It might be hypothesized that membranes which rupture prematurely are inherently "weaker" than those which do not. Over the past 100 years, several investigators have studied the mechanical properties of the chorioamniotic membranes. Poppel[1] in 1863 and Duncan[2] in 1868 studied the bursting tension of the membranes in attempts to delineate the forces of labor. More recent investigations of the physical properties of the membranes have centered on rupture tension[3–6] and membrane thickness.[5, 6] The findings in all of these studies have consistently failed to document significant differences between prematurely and non–prematurely ruptured membranes.

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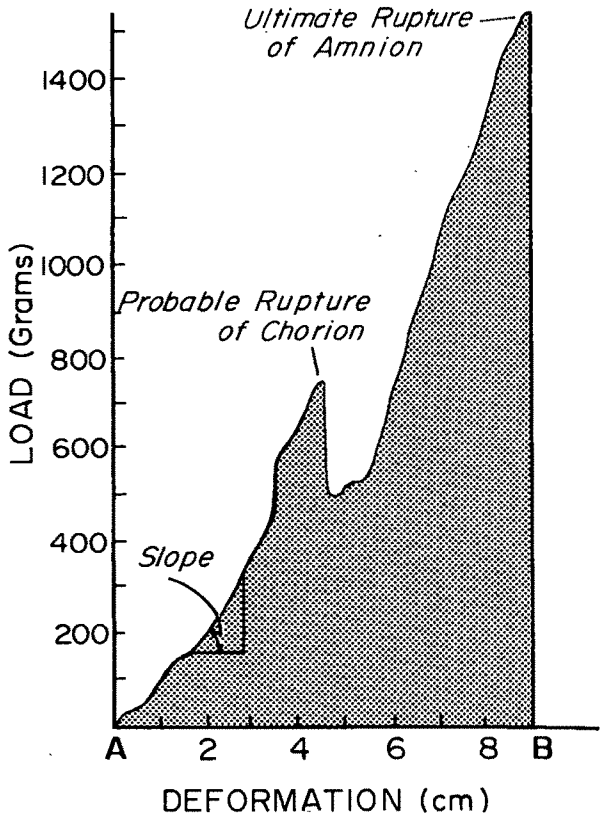


Fig. 1. This typical load deformation curve was obtained during this study. Deformation begins at point *A*, as the membrane starts to be stretched. *Stress* is calculated from the load; strain is calculated from deformation. The material is in the *elastic region* until immediately before chroionic rupture, when it enters the *plastic region. Young's modulus* (of elasticity) is calculated from the slope of the tangent of the curve at any point. *Work to rupture* is represented by the area under the curve (shaded). *Strain to rupture* is calculated from the deformation reached at the point of rupture of the amnion (point *B*). *Rupture tension* is the load per unit membrane width at the point of ultimate rupture (point *B*).

One possible interpretation of these findings is that there are, indeed, no differences. However, acute bursting tension (rupture tension) is only one of several properties which can be measured for materials like the membranes and it may not be the most appropriate one to examine. This study was designed to investigate several properties of the membranes. It is our purpose in this paper to present an approach to studying some of these properties and the preliminary results of our studies.

Background and definitions

If a material, like the chorioamniotic membranes, is stretched and the force is plotted against the amount of stretch, a load-deformation curve results (Fig. 1). Key points on the curve are examined and used to characterize the section of membranes under study by obtaining the following parameters.

Normal stress. This is defined as the load per unit cross-sectional area of a piece of material, where the load is perpendicular to that area.

Normal strain. When a stress is applied, a material generally responds by changing in length. The strain is the change in length (deformation) divided by the length of the material before the stress was applied.

Elastic region. This is the portion of the stress-strain characteristic for a material over which the relationship between stress and strain is reversible. When the stress is relaxed, the material will return to its original length.

Plastic region. Once a material has been stressed to the extent that it enters the plastic region of the curve, it will not return to its original unstressed length when the stress is relieved. Often an increase in stress produces a much greater increase in strain in this region than it does in the elastic region.

Modulus of elasticity (Young). This parameter expresses the stiffness of a given material. It is defined by the slope of the load-deformation curve.

Work to rupture. This parameter is related to two factors, the strength and deformability of a material. This value, assessed by measuring the area under the curve, represents the amount of work done on the material necessary to elicit rupture.

Strain to rupture. This is a measurement of both the elastic and ductile capability of a material; it is defined by the total change in length of a membrane at the point of rutpure.

Rupture tension. This is defined by the maximal load attained at the point of ultimate rupture per unit width of membrane.

Methods

Techniques. Membrane thickness was measured using the techniques described by Polishuk and associates.[5] As shown in Fig. 2, an electrically insulated micrometer barrel is used to contact the top surface of a fetal membrane sample spread out on a metal block. An electronic continuity detector indicates when the micrometer tip touches the surface of the membrane.

The stress-strain characteristics of the membrane samples were determined with the specially constructed testing machine shown in Fig. 3. This consists of a Harvard pump in which the syringe has been replaced by an adjacent trough. A set of jaws for clamping the membrane sample is attached to the syringe plunger support on the Harvard pump, so that it moves uniformly when the pump is operated. A variable resistance device (potentiometer) is attached to

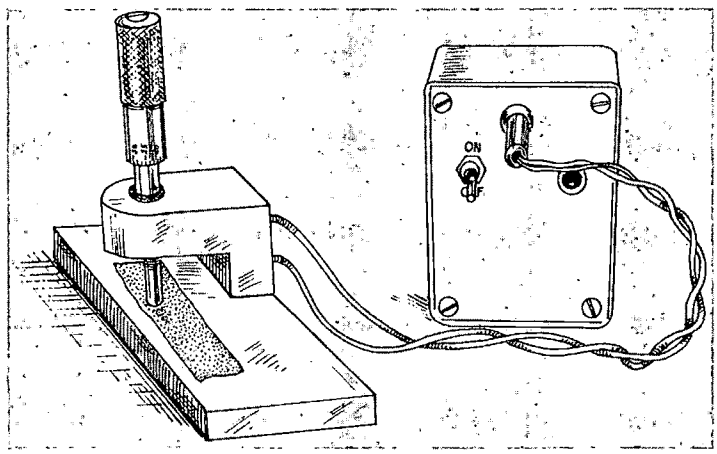


Fig. 2. Thickness of the membrane is determined using a specially constructed micrometer. Contact of the micrometer barrel with the membrane surface is indicated by a light which shows electrical continuity.

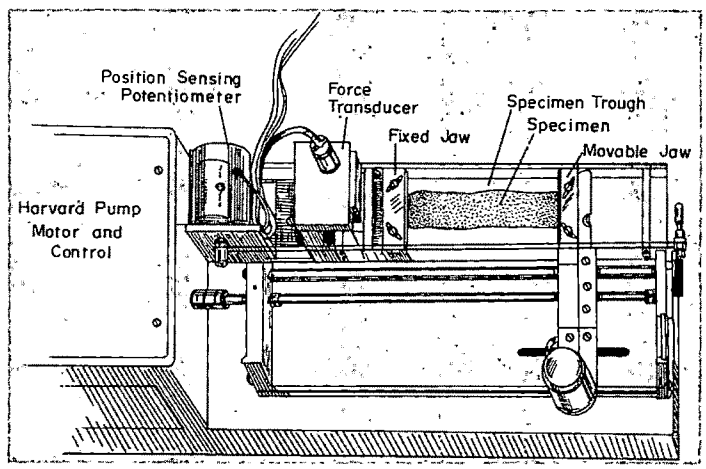


Fig. 3. This device is used to determine the load-deformation characteristics of chorioamniotic membrane samples. For an X-Y plotter, load is obtained from the force transducer and deformation from the position-sensing potentiometer.

the movable set of jaws with steel wires, so that its position can be electrically determined. A second set of jaws, located opposite the first set, is fixed to a vertically oriented cantilever type load cell having foil strain gauge sensing elements. This serves as the force transducer for measuring tension as the specimen is stretched. The electronic signals obtained from the position and force transducers are recorded with an XY plotter on the X and Y axes, respectively.

Materials. A total of 28 gestational sacs were obtained from uncomplicated term pregnancies immediately after vaginal delivery. Of these, 13 sacs had ruptured prematurely, i.e., prior to the onset of labor, and 15 had ruptured spontaneously during labor. There were no other important clinical differences between the two groups of patients.

The specimens were prepared at a constant room temperature of 21° C. and the time since delivery recorded. Multiple 3 cm. wide samples were cut from each chorioamniotic sac with a disposable microtome. Samples were obtained from both the region adjoining the placenta and the area of the rupture site, oriented parallel with each. Membrane thickness was determined.

Membrane samples were then clamped between the jaws of the testing machine, which had been set at a separation of 10 cm. The machine was started and the membrane slowly stretched at a uniform rate of 0.11 cm. per second. Samples were tested either in a dry environment or completely immersed in 0.9 per cent sodium chloride solution at 37°C. Data obtained from the load-deformation curves recorded by the X-Y

Table I. Comparison of prematurely and non–prematurely (spontaneously) ruptured membranes from term pregnancies for various physical properties

	PROM		*SROM*		
	No.	*Mean ± S.D.*	*No.*	*Mean ± S.D.*	*P*
Thickness (mm):					
Near rupture site	13	0.637 ± 0.101	15	0.796 ± 0.159	<0.05
Near placenta	11	0.730 ± 0.091	14	0.818 ± 0.176	N.S.
Work to rupture (Kg.):					
Near rupture site	7	32.4 ± 27	9	55.0 ± 61	N.S.
Near placenta	8	33.5 ± 28	11	55.7 ± 44	N.S.
Strain to rupture (%):					
Near rupture site	7	71.0 ± 26.5	9	84.0 ± 39.0	N.S.
Near placenta	8	101.7 ± 55.3	11	82.1 ± 21.0	N.S.
Modulus of elasticity (maximal value on plotted curves):					
Near rupture site	7	12.78 ± 12.35	9	19.31 ± 18.31	N.S.
Near placenta	8	6.22 ± 4.89	11	20.86 ± 25.02	<0.01
Modulus of elasticity (at breaking point):					
Near rupture site	7	7.12 ± 8.74	9	11.98 15.93	N.S.
Near placenta	8	2.33 ± 2.00	11	9.19 7.73	<0.05

Table II. Comparison of rupture (bursting) tensions of chorioamniotic membranes measured by various investigators

				Rupture tension	
Year	*Ref. No.*	*Investigator*	*Membranes studied*	*Original units*	*Converted units (mean ± S.D., Kg./cm.)*
1863	1	Poppel	Unselected	1.37 lb.	0.174
1868	2	Duncan	Unselected	1.19 lb.	0.151
1953	3	Danforth	"Weak"	25 cm. Hg /cm.	0.340
			"Strong"	24 cm. Hg/cm.	0.326
1954	4	Embrey	"Early and Late" rupture	168,900 dynes/cm.	0.172
1962	5	Polishuk et al.	"Normal"		0.205
1964	6	Polishuk et al.	PROM		0.299
			SROM		0.207
1975		Artal et al.	PROM near rupture		0.454 ± 0.405
			PROM near placenta		0.446 ± 0.470
			SROM near rupture		0.629 ± 0.650
			SROM near placenta		0.850 ± 0.647

plotter were analyzed and differences tested statistically with an F test and the appropriate t test.[7, 8]

Results

The results presented in Table I are limited to those samples evaluated in saline less than 1 hour after delivery. A dry environment and a prolonged interval from delivery to testing were found to be inappropriate conditions for study of chorioamniotic membranes, since both were found to affect the mechanical characteristics of the samples. The statistical distribution of values for each parameter was examined and found in all cases to be normal or consistently mildly left asymmetrical. Variances were generally large. Significant differences between prematurely and non–prematurely ruptured membranes included the following: Near the rupture site, samples from the prematurely ruptured membranes were thinner than those from membranes which had ruptured spontaneously (mean = 0.637 and 0.796 mm., respectively, $p < 0.05$). The modulus of elasticity near the placenta, measured both as the maximal tangential slope on the curve and at the breaking (rupture) point, was lower for prematurely than for spontaneously ruptured

membranes ($p < 0.01$ and <0.05, respectively). Differences in other parameters were not statistically significant.

Comment

This study was designed to evaluate the hypothesis that there may be measurable differences between chorioamniotic membranes which have ruptured prematurely and those which have not. Previous investigations have failed to demonstrate any differences, when comparing rupture tension as the only parameter under consideration.[3-6]

Table II compares the rupture tensions reported in previous investigations with those of the present study. Rupture tension, as measured with the present device, was similar, but somewhat more than those obtained in previous investigations. This may be explained by differences in techniques. All previous tests utilized biaxial stresses, inflating a membrane sample like a balloon, whereas in the present test the material is stressed in only one direction, uniaxially. No statistically significant differences in rupture tension between prematurely and spontaneously ruptured membranes were found. Our results are also in agreement with previous investigations,[9] which showed considerable variability in this measurement between gestational sacs and in different areas of the same sac.

In previous investigations,[5, 6] membrane thickness was not reported as a function of original location near either the rupture site or placenta. In the present study, the thickness of the membranes was found to be reduced near the rupture site in PROM. It is possible that this thinning may be an effect of the previous rupture and not of etiologic significance. On the other hand, it may be speculated that the thinning might represent a local phenomenon related to a chronic stress during pregnancy, which slowly produces changes in the membranes.

The modulus of elasticity, measured as a maximal value and at the breaking (rupture) point on the load-deformation curve, was reduced for prematurely ruptured membranes sampled from the periplacental area. This might be interpreted physiologically to suggest that for the same stress, prematurely ruptured membranes demonstrate more strain than non–prematurely ruptured membranes. Alternatively, prematurely ruptured membranes develop the same strain as non–prematurely ruptured membranes at lower stress. The modulus of elasticity measured near the rupture site tended to be lower in PROM, but the difference from non–prematurely ruptured membranes was not significant.

This is a preliminary study. The results suggest, however, that there may be inherent differences between membranes which rupture prematurely and those which do not, if appropriate parameters are measured. Further investigations are warranted to confirm these findings and to examine the clinical implications with respect to the etiology of PROM.

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Automatic balance for fetal weight studies

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An automatic balance was constructed of aluminum sheet, miniature ball bearings, and a strain gauge. The balance was capable of measuring 1 to 4 kg. with an accuracy of ±0.5 Gm. and a 95 per cent response time of <0.3 seconds. Fetuses of term ewes were exteriorized and weighed continuously for up to 3 hours. Rapid depletion of the ewe's blood volume led to a 10 to 24 per cent increase in estimated fetal blood volume. Fetal weight loss occurred regularly during reversible occlusion of the umbilical veins.

THE PREGNANT sheep has become a useful model animal for fetal and placental studies. In many experimental protocols, the lamb fetus is exteriorized and sustained by an intact placental circulation. When precautions are taken to avoid maternal hypoxia, to prevent the fetus from breathing, and to keep it warm, the preparation will be viable for several hours.

Occasionally, however, we have noted in exteriorized fetuses varying degrees of congestion in the central veins. Although the cause of the engorgement remains to be determined it may derive from the placenta. There is an abundant clinical literature showing that significant amounts of blood can pass from placenta to the delivered infant when clamping of the umbilical cord is delayed.[4, 11, 12]

In the present paper we describe a sensitive automatic balance with which the quantitative evaluation of this exchange of mass can be made.

Methods

A. Construction and operational characteristics of the balance. The weighing and balancing arms of the beam were machined from 0.25 inch aluminum sheet and fitted with six miniature bearings (Reed Inst. Bearing Co., SD1624ZE51) (Fig. 1). One bearing serving as the fulcrum was placed 5 cm. from the end of the weighing arm. The balancing arm was doubled back on itself and was supported by a column containing another bearing. Fitted to the end of this second beam was a yoke through which ran the first section of balancing arm. Attached to the yoke was a strain gauge (Stratham, G18-350, capacity ±230 Gm.). The ratio of weighing arm to balancing arm lengths was approximately 1:7.

The result of doubling back the balancing arm was a rather compact unit which did not show inertial changes due to air movements or vibrations transmitted from the floor to the balance. A lightweight aluminum rack (20 by 50 cm.) onto which the fetus would be placed was suspended from the weighing arm by four 60 cm. lengths of bead chain. The balance was bolted to a 5 foot high structure made of slotted steel angle which was anchored securely to the concrete floor.

To avoid the placement of prohibitive strains on the strain gauge during calibration procedure or during actual weighing of the fetus, a 500 Gm. lead weight was added to a sliding tray on the balancing arm. This tray could be secured at any desired place on the arm to effectively cancel all or most of the weight placed on the aluminum rack.

The response time and sensitivity of the system was determined by loading the rack with 1 to 4 Kg. weights and counterbalancing. Then 0.5 to 20 Gm. weights were gently placed on the rack as the recorder chart paper traveled at 1 inch per second. Stability of the

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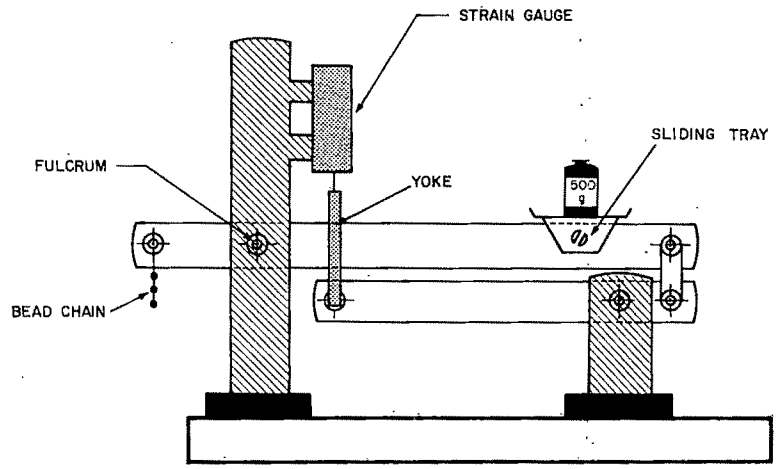
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Fig. 1. Artist's drawing of side view of weighing machine.

system was determined by placing weights on the rack and observing the recording for 1 hour.

B. Animal experiments. Fifteen pregnant ewes with known gestation dates were each anesthetized with methoxyfluorane (Metafane, Pitman-Moore) and placed on intermittent positive pressure ventilation with 100 per cent oxygen. Fetuses were delivered through a midline abdominal incision and placed in an insulated box after the head was covered with a saline bag. The body was well insulated with a plastic bag and several dry turkish towels. The ewe was rotated on her side and the box was carefully placed on a platform suspended from the balance, due care being taken to avoid cooling, drying, or stretching the umbilical cord. The operating table was then raised or lowered until the vertical position of the fetal body with respect to the ewe corresponded to its original position in utero. Fetal weight was recorded continuously for 20 to 40 minutes prior to any further experimental procedure. As a second check on the calibration of the system, five 10 Gm. weights were added in sequence to the loaded rack containing the fetus. The deflection of a pen of the recording potentiometer (Hewlett-Packard, 7100 B) was noted.

Three to 5 ml. of formalin were injected into the perivascular tissue of the umbilical veins and they were exposed by dissection. A 3 to 5 second total occlusion of these veins with a No. 1 silk thread was followed immediately by a reduction in fetal weight as umbilical arterial blood continued to be pumped to the placenta. The rate of weight change in the first second divided by the fetal weight was taken as a measure of the umbilical blood flow rate. Umbilical blood flow rate was measured by this procedure between three and 12 times in each of 15 fetuses. Values were averaged for each fetus prior to determining the mean and standard error of the mean for the whole group.

Table I. Weight gained by exteriorized fetus during terminal hemorrhage of ewe

Ewe	*Final fetal weight (Gm.)*	*Weight gained (Gm.)*	*Estimated percentage gain in blood volume* (%)*
27R	2,780	70	25
9R	3,260	33	10
40R	3,900	60	15
58Y	3,735	57	15
54Y	2,950	60	20
35Y	4,420	59	13
16W	2,960	30	10
172Y	2,680	45	17
193	1,840	38	21

*Based on a fetal blood volume of 10 per cent of body weight.[8]

As a check on the possible error introduced by misreading the weight loss curves, eight to 13 occlusions were made at 30 second intervals in three fetuses and calculations of the rate of weight loss during the first second were made from the strip chart record independently by two investigators.

In two of the 15 fetuses heparin-filled catheters (internal diameter 0.027 inch) were placed in the descending aorta (via femoral artery) and in the central venous circulation (via femoral vein) at the junction of the inferior and superior vena cava. By means of a strain gauge pressure transducer and a strip chart recorder fetal blood pressure and fetal heart rate (as judged by oscillations in the pressure recording) were measured before and during occlusion of the umbilical veins. In nine of the 15 ewes, after completion of the occlusion trails, a large-bore catheter was inserted

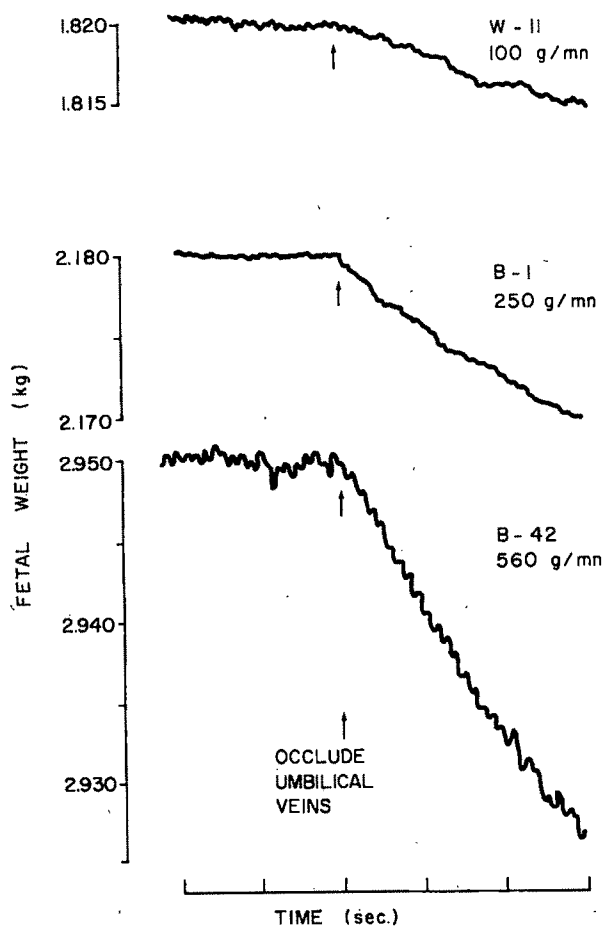


Fig. 2. Three representative records of fetal weight during occlusion of umbilical veins.

proximally in the external carotid artery. Fetal weight was monitored during depletion of the ewe's blood (2 to 3 L. in 1 minute).

Results

The sensitivity of the weighing machine, as judged by multiple determinations of recorder deflection following addition of various weights, was ±0.5 Gm. In repeated trials in which 20 Gm. weights were added to the loaded and counterbalanced system, we found a 90 per cent response time of <0.3 second. A 20 Gm. weight was chosen because the fetal weight change never exceeded 20 Gm. during the first 2 seconds of occlusion. The magnitude of the load from 1 to 4 Kg. had no discernible effect on the response time. Drift of recording was <1 Gm. per hour, or about 0.05 per cent of a 2 Kg. load.

Table I indicates the umbilical blood flow rates determined in three experiments and calculated independently by two investigators. Mean values for both investigators did not differ, indicating that neither investigator was consistently higher nor lower than the other. The within-fetus correlation between estimations taken at the same time by the two investigators was 0.816. Some of the differences were related to judging the weight loss curve which had superimposed on it occasional oscillations due to inertial changes of fetal heart origin. This was especially noticeable in large robust fetuses with high umbilical blood flow rates. Three representative records of fetal weight during occlusion of the umbilical veins are given in Fig. 2. Umbilical blood flow rates (15 animals) were 215 ± 16 S.E.M. Gm./Kg.-min.

Rapid removal of the maternal blood was followed by a significant increase in fetal weight by amounts ranging from 33 to 70 Gm. (Table II). Occlusion of the umbilical veins did not produce any noticeable lasting effects. Weight was re-established to control levels within a few seconds following release of occlusion (Fig. 3). Fetal aortic pressures dropped no more than 1.5 mm. Hg and there was no change in pulse pressure during the first second of the occlusion. Decrease in central venous pressure during this time never exceeded 0.6 mm. Hg.

Comment

Since the classic experiments of Sanctorius,[13] weight changes have been used to great advantage in understanding various exchanges which occur between man and animals and their environments.[1] The technique of continuous weight recording has also proved useful in studying circulatory physiology of the nonpregnant uterus.[2, 3] In this paper, we have described a technique for weighing an exteriorized fetus. The balancing system can be used to study the partitioning of fetal blood between placenta and fetus following various experimental procedures. However, to date it has not been used to study position-related partitioning of the fetoplacental blood volume. Since the weight transducer measured strain, there was virtually no change in vertical position of the fetus during the weighing procedure.

A common observation in most experiments was the gradual increase in fetal weight following exteriorization of the fetus and its placement on the balance. The rate of rise was variable but usually linear (<1 Gm. per minute). The linearity of the phenomenon suggested to us that it was related to the steady accumulation of blood and tissue water, but no analyses of blood or tissue were made in this study. The duration and amount of increase in weight were never determined exactly, since we began other procedures after 20 to 40 minutes.

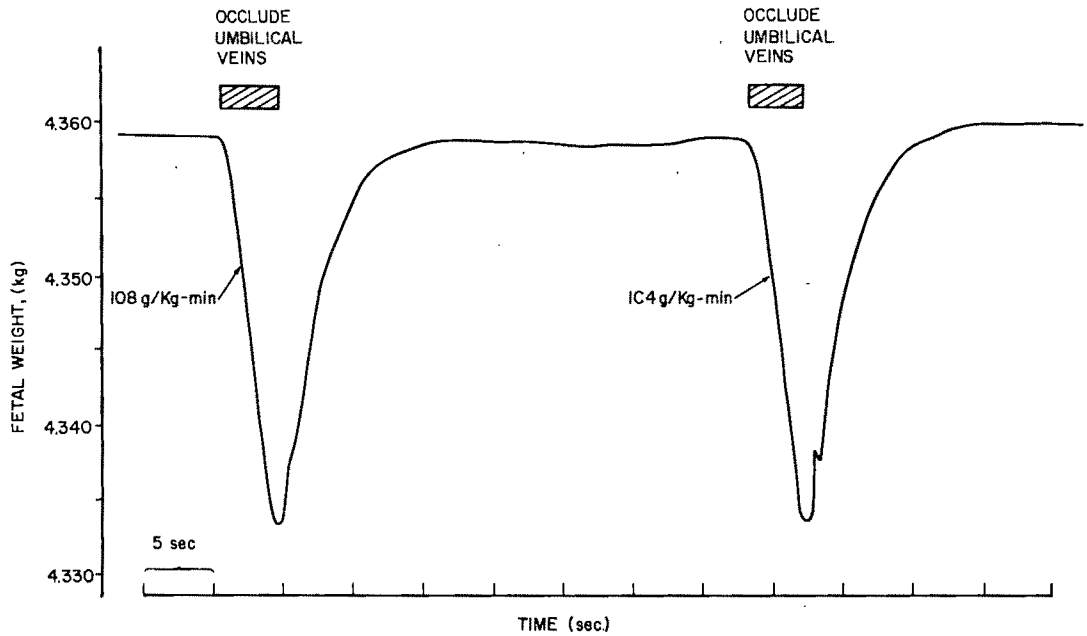


Fig. 3. Record of fetal weight showing return of weight to control levels a few seconds following release of occlusion of umbilical veins.

Table II. Umbilical blood flow rates calculated from successive weight loss curves in three exteriorized fetuses*

Fetus Y-233 (2.22 Kg.)		*Fetus B-42 (2.95 Kg.)*		*Fetus B-1 (2.18 Kg.)*	
A (Gm./min.)	*B (Gm./min.)*	*A (Gm./min.)*	*B (Gm./min.)*	*A (Gm./min.)*	*B (Gm./min.)*
204	204	500	496	306	280
176	187	545	570	250	252
215	204	610	590	210	222
182	181	560	590	275	250
193	195	575	510	270	273
176	179	570	570	225	250
187	184	460	475	275	285
187	190	510	495	260	250
		550	535	260	262
		500	501	245	248
		490	482	195	228
				295	276
				265	268

*Three- to five-second occlusions of both umbilical veins were made every 30 sec. Calculations were made independently by two investigators, A and B.

Rapid gain in fetal weight during terminal hemorrhage of the ewe may have been due to a fetal transfusion of placental blood. Presumably, maternal hypoxia led to a uterine contraction which facilitated the return to the fetus of umbilical venous blood while at the same time producing a marked increase in placental vascular resistance. Indeed, on postmortem examination of the hemorrhaged ewe, the uterus was always contracted and the central venous pool of the fetus was greatly distended. A contributory factor may have been a hypoxia-induced failure of the fetal heart with resultant diminution of umbilical arterial blood flow.

An advantage of the system for fetal weighing is that it appears to be useful as a means for measurement of umbilical blood flow although, in the absence of confirmatory data by other techniques, a firm conclusion as to its usefulness cannot be made. No surgery needs to be performed on the fetus and its circulation system is left intact. In many respects the estimation of blood flow by weight change is similar to the recording of volume change.[5-7] Many of the factors necessary for

success are shared by both techniques. Of perhaps greatest importance is the need to make an estimate of the rate of volume or weight change before a significant decrease occurs in the umbilical arterial pressure.[9, 10] In our experiments the very small decrease in central venous and fetal femoral artery pressure may have produced a slight underestimation of the umbilical blood flow rate. These pressure changes reflect the variable amount of loss in blood volume and its effect on cardiac output. The greatest loss in weight of any fetus during the first second of occlusion was 8.9 Gm. Assuming a blood volume of this fetus of 10 per cent of its body weight[8] or 295 Gm., only 8.9/295 or 3 per cent of the blood volume would have been lost during the first second. The linear nature of the weight decrease would argue also against any significant reduction in umbilical blood flow rate during the first second.

The results of these experiments show that considerable changes in weight can occur in the exteriorized sheep fetus with umbilical circulation intact but no conclusion can be made as to whether or not the weight changes represent a repartitioning of fetoplacental blood or result from transfer of fluid, perhaps water, from mother to fetus. Since the exteriorized fetal preparation is used regularly in physiologic and pharmacologic research, such information on weight changes may be important in evaluating experimental results. The extent to which they mimic the changes in the newborn infant remains to be determined.

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Post–paracervical block bradycardia: Its prediction and preventability

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The fetal heart rate recordings of 100 parturients given PCB with less than 200 mg. of lidocaine were reviewed. No PCB bradycardia occurred if there were no pre-PCB FHR decelerations (92 per cent accuracy). In an effort to prevent post-PCB bradycardia, atropine was given in the maternal paracervical area and also intravenously. The most effective dose was 1.0 mg. intravenously, but the prophylactic efficiency of atropine was uncertain in preventing the post-PCB bradycardia.

THE OCCURRENCE of significant fetal bradycardia after paracervical (PCB) anesthesia during labor has been recognized as a worrisome after effect of this type of intrapartum pain relief. Previously, we convinced ourselves that the type of fetal heart rate (FHR) response to various uterine stimuli (unless severe) was mostly determined by the level of fetal arousal. For example, if a FHR recording showed marked baseline variability and accelerations, the fetus was considered "highly aroused" and would act accordingly; by contrast, when there was a relatively flat baseline and reduced beat-to-beat variability in the FHR recording, the fetus was considered to be "asleep."[1] In this study, we initially assumed that arousal levels likewise determined FHR changes after PCB.

We first estimated the pre-PCB fetal arousal level from the FHR responses to uterine contractions and using this information, we predicted what FHR change would occur following a paracervical block. A second portion of the study was to test whether atropine injected intravenously or into the paracervical area would modify the occurrence of post-PCB fetal bradycardia.

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Table I. FHR bradycardia after PCB

Chart review	*Present*	*Questionable*	*Absent*
Predicted* correctly	13	2	77
Predicted incorrectly	3	3	2
Total	16	5	79

*Assumption is that post-PCB bradycardia is present when pre-PCB decelerations are present and absent when they are absent.

Method

Paracervical studies. The FHR recordings of 100 parturients who received a PCB with lidocaine in amounts of 120 to 200 mg. at one time were reviewed without knowledge of their FHR patterns following the block. The FHR patterns before the PCB were classified according to whether the fetus was highly aroused, or whether it was barely aroused, or whether it was "asleep." If decelerations of FHR occurred during uterine contractions (type I dips) the bradycardia was initially classified according to its duration and to severity (decrease of rate).

In the evaluation of the post-PCB bradycardia, a positive response to the injection was defined as an initial heart rate decrease of greater than 20 b.p.m. and lasting at least 30 seconds usually followed by a few late or other decelerations. Other post-PCB bradycardia (abrupt and brief, prolonged and irregular, etc.) were considered questionable as to their etiologies.

Atropine studies. Sixty women in labor having type I dips were informed of the nature of the study. In 30 of

Table II. FHR bradycardia after PCB plus atropine when type I dips present

Maternal drug route	*Atropine dose*		*Total*
	0.5 mg.	*1.0 mg.*	
Intravenous	2/6 (33%)	1/6 (17%)	3/12 (25%)
Paracervical	5/6 (83%)	3/6 (50%)	8/12 (67%)
Total	7/12 (58%)	4/12 (33%)	11/24 (46%)

Table III. Per cent FHR "atropine" effect

Maternal drug route	*Atropine dose*		*Total*
	0.5 mg.	*1.0 mg.*	
Intravenous	6/12 (50%)	10/12 (85%)	16/24 (66%)
Paracervical	3/18 (16%)	13/18 (72%)	16/36 (44%)
Total	9/30 (30%)	23/30 (77%)	32/60 (53%)

these parturients, 0.5 mg. of atropine was given in divided doses either intravenously to the mother or in her paracervical area. In another 30 parturients, the dose of atropine was increased to 1.0 mg.

Twelve other women who were having type I decelerations were given a PCB with 120 to 200 mg. of lidocaine plus atropine. Another 12 women received a similar PCB except that the atropine was given intravenously.

Results

The degree of severity of the pre-PCB episodes of type I decelerations appeared to be of no significance. Therefore, the data were pooled and any FHR pattern showing type I dips of greater than 20 b.p.m. decrease or longer than 20 seconds was considered positive for "pre-PCB bradycardia." Four of the five questionable post-PCB heart rate changes occurred in the terminal stages of labor.

The estimation of prior PCB fetal arousal levels was of no value in predicting the occurrence of post-PCB FHR accelerations or loss of beat-to-beat variability. But as shown in Table I, we were more than 80 per cent accurate in predicting which fetus would develop a post-PCB bradycardia. Furthermore, we were able to predict which fetuses would have no post-PCB fetal bradycardia with 92 per cent accuracy.

Among the six parturients who had prior type I dips (Table II) and were given 0.5 mg. of atropine with the lidocaine in the paracervical area, five had post-PCB bradycardia. Two of these FHR recordings showed a "fetal atropine effect" (loss of beat to beat variability and sometimes tachycardia).[2] When the atropine paracervical dose was increased to 1.0 mg. and a PCB given, five of six subsequent FHR patterns showed a "fetal atropine effect" and only two had a post-PCB bradycardia.

Five out of six recordings showed an "atropine" effect and only one had a post-PCB bradycardia when the patient was given 1.0 mg. atropine intravenously after prior type I dips and a PCB. The comparable figures for the 0.5 mg. intravenous dose was four out of six with "atropine" effect and three out of six demonstrated post-PCB bradycardia.

The FHR effects of the PCB aside, the 1.0 mg. atropine doses were much more effective in producing FHR recordings with loss of beat to beat variability than was the 0.5 mg. dose (77 vs. 30 per cent) (Table III). The maternal intravenous route appeared to be more effective than the paracervical area (66 vs. 44 per cent). Maternal atropine symptoms (increased heart rate, dry mouth) were always present whenever there was a fetal atropine effect.

Comment

In this particular study, we limited our review of records to cases in which less than 200 mg. of lidocaine were used which probably explained our low incidence (4.0 per cent) of post-PCB bradycardia when there were *no* prior dips. It also seems clear that if there *are* pre-PCB decelerations, there will probably (81 per cent) be post-PCB bradycardia even at this low dose level of lidocaine.

The second part of this study suggests that there is no advantage in using the paracervical area vs. the maternal intravenous route for fetal drug therapy, that fetal atropine symptoms occur only at those levels when maternal atropine symptoms occur, and that use of atropine in prophylaxis of PCB bradycardia is uncertain.

The decreased efficiency of the paracervical area as a portal for fetal drug therapy was unexpected in view of studies showing greater fetal blood concentration of PCB agents than occurred in the maternal blood.[3] With a drug such as atropine, which crosses the placenta relatively rapidly, the maternal compartment must be saturated in order to maintain a therapeutic level in the fetal compartment. Administering the drug directly to the fetus would therefore achieve only a temporary fetal therapeutic advantage in comparison to giving it to the mother. Nevertheless, the paracervical route seemed worthy of testing in terms of rapidity of onset of fetal atropine affects.

Atropine was selected for study as it prevents the bradycardia of vagal origin. The PCB "bradycardia" can represent either vagal activity, or decreased cardiac performance due to drugs, hypoxia, etc. Because fetal

cardiac output decreases during prolonged fetal bradycardia, asphyxia can occur in association with PCB "bradycardia" regardless of their etiology. Thus, atropinization can give us much information about the etiology of these bradycardias, provided the results are consistent.

The reasons for atropine to have failed to protect against the post PCB bradycardia are many and include: (1) lidocaine decreases fetal myocardial function, (2) PCB does decrease uterine artery perfusion and may aggravate placental hypoperfusion during uterine contractions,[4] (3) lidocaine may effect placental transport of oxygen and carbon dioxide.

At any rate, it would appear that with use of minimal anesthetic agent, it is possible to predict with a high degree of accuracy which fetuses will show post-PCB heart rate decelerations or bradycardia. We predict that if those fetuses which are free of decelerations of heart rate associated with uterine contractions alone are given minimal dose PCB's, then the incidence of post-PCB decelerations will be virtually eliminated. These concepts of proper patient selection seem more appropriate than attempting to inhibit abnormal FHR responses with atropine. For while the incidence of post-PCB bradycardia with prior type I dips was reduced from 15/17 (Table I) to 3/12 by adding 1.0 mg. of atropine (Table II), this improvement does not compare to the 6/83 rate when *no* prior type I dips were present (Table I).

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Hyaline membrane disease in twins

A 7 year review with a study on zygosity

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We reviewed 294 pairs of twins born from January, 1966, to December, 1972. In 19 pairs one or both members developed hyaline membrane disease (HMD). Of these, both twins were affected in 12 pairs, twin B alone in six pairs, and twin A alone in one pair. The group affected (19 pairs) had lower gestational age, birth weight, Apgar score, increased incidence of monozygotic (MZ) twins, and higher mortality rate than the group without HMD (275 pairs). MZ twins were more immature than dizygotic (DZ) twins ($p < 0.02$). When both twins were affected they had lower gestational age, birth weight, and increased monozygosity than when B alone was affected ($p < 0.05$). When twin B alone was affected, he had lower Apgar score than twin A ($p < 0.05$). We suggested that (1) HMD occurs in twins because of lung immaturity, as it does in singletons; (2) monozygosity may be a predisposing factor to HMD because of the associated prematurity; and (3) the greater risk of twin B is probably related to birth asphyxia.

BECAUSE TWINS tend to be born prematurely, they are at high risk of developing hyaline membrane disease (HMD). More frequently, both twins are affected. When only one twin is affected, this is usually twin B.[1, 2] Unfortunately, most of the studies available have been on autopsy material and we do not know what factors determine the predominant involvement of both twins over either twin A or B alone, or of twin B over twin A. Furthermore, the role of zygosity in predisposing twins to HMD is unknown.

We designed this study to define the role of maternal age, parity, bleeding, placenta morphology, and twin's gestational age, birth weight, sex, Apgar score, zygosity, and mode of delivery as predisposing factors of HMD in twins.

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Materials and methods

From January, 1966, to December, 1972, 294 pairs of twins were born out of 27,284 pregnancies (1:93 pregnancies) at the Women's Centre, Winnipeg. In 19 pairs one or both members developed HMD. Of these, both twins were affected in 12 pairs, twin B alone in six pairs, and twin A alone in one pair. Therefore, 31 out of 588 twins were affected, giving an incidence of HMD in twins of 0.05 (1:20 liveborn twins). The diagnosis of HMD was made by clinical findings, x-ray, and analysis of blood gases and pH. All chest x-rays were reviewed by one radiologist. Severity of the disease was estimated as mild, moderate, or severe, according to the degree of parenchymal involvement.

In the whole population of twins (294 pairs) we made the following analysis (1) In the groups with and without HMD we compared maternal age, parity, bleeding, placenta morphology, and twin's gestational age, birth weight, sex, Apgar score (1 minute), zygosity, mode of delivery, and mortality rate. Zygosity was determined by sex, placenta morphology,[3] and blood groups in 14 pairs with and 57 pairs without HMD. (2) We compared the same variables in 12 pairs with

Table I. Comparison of different variables in groups with and without HMD

Variables	*No HMD (275 pairs)*	*HMD (19 pairs)*	*p*
Mother:			
Age (yr.)	27 ± 3 (mean ± S.E.)	27 ± 1	N.S.
Parity	3.3 ± 0.1	2.7 ± 0.2	N.S.
Bleeding	6	3	N.S.
Placenta:			
Diamniotic dichorionic	122/173 (70%)	7/17 (41%)	<0.025
Diamniotic monochorionic	44/173 (25%)	10/17 (59%)	<0.025
Monoamniotic monochorionic	7/173 (5%)	0/17 (0%)	N.S.
Twins:			
Gestational age (wk.)	38 ± 0.2	31 ± 0.7	<0.001
Birth weight (Gm.)	2490 ± 380	1460 ± 485	<0.001
Sex (M/F)	1.27	0.81	N.S.
Apgar score (1 min.)	7.5 ± 1.5	5.4 ± 0.5	<0.001
Monozygosity	20/57 (35%)	10/14 (71%)	<0.025
Mode of delivery			
Vertex	339/535 (63%)	21/38 (55%)	N.S.
Breech	177/535 (33%)	11/38 (29%)	N.S.
C-section	19/535 (4%)	6/38 (16%)	<0.001
Mortality rate	9/550 (2%)	19/38 (50%)	<0.001

Table II. Comparison of different variables in groups with both twins and only twin B affected

Variables	*A and B affected (12 pairs)*	*Only B affected (6 pairs)*	*p*
Mother:			
Age (yr.)	28 ± 2 (mean ± S.E.)	24 ± 1	N.S.
Parity	2.9 ± 0.7	1.8 ± 0.5	N.S.
Bleeding	2	1	N.S.
Placenta:			
Diamniotic dichorionic	4/10 (40%)	3/6 (50%)	N.S.
Diamniotic monochorionic	6/10 (60%)	3/6 (50%)	N.S.
Monoamniotic monochorionic	—	—	
Twins:			
Gestational age (wk.)	31 ± 0.7	33 ± 1	<0.05
Birth weight (Gm.)	1320 ± 80	1700 ± 130	<0.02
Sex (M/F)	0.85	0.5	N.S.
Apgar score (1 min.)	5.5 ± 0.6	5.5 ± 0.5	N.S.
X-ray			
Mild	9/24 (37%)	2/5 (40%)	N.S.
Moderate	4/24 (17%)	1/5 (20%)	N.S.
Severe	11/24 (46%)	2/5 (40%)	N.S.
Monozygosity	8/8 (100%)	2/5 (40%)	<0.001
Mode of delivery			
Vertex	14/24 (58%)	6/12 (50%)	N.S.
Breech	6/24 (25%)	4/12 (33%)	N.S.
C-section	4/24 (17%)	2/12 (17%)	N.S.
Mortality rate	14/24 (58%)	4/12 (33%)	N.S.

twins affected and in six pairs with only B affected. (3) We also compared birth weight, sex, Apgar score, mode of delivery, and mortality rate between twins A and B when B alone was affected.

Results

Twins with HMD in one member at least had significantly lower gestational age, birth weight, Apgar score at 1 minute, increased incidence of monozygosity, mortality rate, and higher incidence of cesarean section than twins without HMD ($p < 0.025$; Table I). Diamniotic monochorionic placentas were more frequent and diamniotic dichorionic placentas less frequent in the group with HMD ($p < 0.025$). Maternal factors were not significantly different in both groups.

When both twins were affected, they had significantly lower gestational age and birth weight, and higher proportion of monozygosity than when B was affected alone ($p < 0.05$; Table II). Maternal factors, placenta, sex, Apgar score at 1 minute, mode of

Table III. Comparison of different variables in twins A and B when only B was affected (6 pairs)

Variables	*A*	*B (affected)*	*p*
Birth weight (Gm.)	1,476 ± 55 (mean ± S.E.)	1,935 ± 222	<0.05
Sex (M/F)	0.2	1.0	N.S.
Apgar score (1 min.)	5.8 ± 0.4	4.2 ± 0.3	<0.05
Mode of delivery			
Vertex	4/6 (66%)	2/6 (33%)	N.S.
Breech	1/6 (17%)	3/6 (50%)	N.S.
C-section	1/6 (17%)	1/6 (17%)	N.S.
Mortality rate	0/6 (0%)	4/6 (67%)	<0.01

delivery, and mortality rate were not significantly different in both groups.

When twin B alone was affected, he had significantly lower Apgar score and higher birth weight and mortality rate than twin A ($p < 0.05$; Table III). Sex and mode of delivery were not significantly different in both groups.

It has been shown that in the general population of twins, monozygotic pairs account for 44 per cent of the total.[3] Because of the increased percentage of monozygotic twins in the population with HMD (Table I), we assessed the concordance rate of HMD in MZ and DZ twins to determine whether a genetic component could be considered in the etiology of HMD. This was 80 per cent and 25 per cent in MZ and DZ twins, respectively ($p < 0.05$).

Comment

We found that: (1) twins with hyaline membrane disease were significantly more immature than twins without HMD, as reflected by their lower gestational age and birth weight; (2) when both twins were affected they were also more immature than when twin B alone was affected; and (3) when twin B alone was affected he had a lower Apgar score at 1 minute and greater birth weight than twin A. These findings suggest that prematurity is the primary determinant of HMD in twins. The more immature they are, the greater will be the chance for both twins becoming affected. The higher risk of twin B with respect to A is probably related to birth asphyxia as reflected by a lower Apgar score at 1 minute. The high association between monozygotic twins and HMD is probably related to the greater immaturity of monozygotic as compared to dizygotic twins.

Our findings support previous observations that twin B is at higher risk than twin A.[1, 2] In 19 pairs with one or both members affected the relative frequency of B over A was 1.4. The incidence of HMD in twins A and B was not significantly different because the number of pairs with only one twin affected was small (n = 7). However, combining our pairs in which only one twin was affected with other similar pairs reported in literature,[1, 2, 4] the number is large enough to show that twin B is significantly more affected than A.

Birth asphyxia probably explains the higher incidence of HMD in twin B. However, because twin A had significantly lower birth weight than twin B when B alone was affected, we also considered the possibility of A being dysmature in relation to B, and, therefore, less susceptible to the disease.[5] But in twins discordant for size, the smaller twin has equal chance of being A or B.[6] Therefore, this argument would be valid only if the incidence of HMD were also equal in twins A and B. This was not so and this hypothesis was untenable.

When both twins were affected (12 pairs), the severity of the disease was similar in seven pairs and greater in twin B than A in five pairs. In no pair was twin A more severely affected than B. During 1973, in a prospective study being conducted in our Neonatal Unit, we had six pairs of twins with at least one twin affected. Of these, both twins were affected in four pairs and twin B alone in two pairs. Twin A alone was not affected. Therefore, these observations strongly suggest that twin A is rarely affected alone and when both are affected, B has more severe disease.

The incidence of monozygotic twins was significantly increased in twins with HMD (Table I). This increase was due to a high incidence of monozygotic twins within the 12 pairs with both twins affected. When B was affected alone, 40 per cent of the twins were monozygotic (Table II). The predominance of monozygotic twins in the group with HMD and the increased concordance rate of HMD in MZ twins might indicate a genetic predisposition to this disease. This has been suggested previously.[4] However, (1) twin B alone was significantly more affected than twin A alone, probably due to birth asphyxia, and (2) MZ twins were at significantly lower gestational age than DZ twins, being at higher risk of developing HMD. Therefore, the high concordance rate for HMD in MZ twins may not represent a genetic component. We may postulate that monozygotic twins are born more prematurely than dizygotic twins[7] because of placentation (usually diamniotic-monochorionic), and consequently are more prone to develop HMD. In other words, monozygosity leads to immaturity and immaturity leads to HMD.

Because of the above considerations, we decided to investigate whether the incidence of HMD in twins could be explained by prematurity alone. Therefore, we compared the incidence of HMD in twins and

singletons born under 35 weeks of gestation during the years 1970 to 1972 (Table IV). The per cent of twins born under 35 weeks of gestation was fivefold the per cent of singletons born in the same period, and they had twice the incidence of HMD than singletons had. This suggests that prematurity alone, irrespective of any genetic component, could explain the higher incidence of HMD in twins. These findings do not support previous observations that the incidence of HMD in twins could not be explained on the basis of prematurity alone.[4] The reason for disagreement is probably twofold: (1) In a previous study twins were selected after rigorous review and clinical evaluation, while singletons were not similarly reviewed, and (2) because the incidence of HMD in twins was sixfold that in singletons, whereas the incidence of prematurity was only fourfold that in singletons, it was concluded that prematurity alone could not explain the increased incidence of HMD in twins. However, term infants were included in the total population of singletons and, therefore, underestimated the incidence of HMD. When we matched singletons and twins for gestational age (Table IV), the incidence of HMD in twins was only double that in singletons.

Table IV. Incidence of HMD in singletons and twins born under 35 weeks of gestation (1970 to 1972)

		Infants < 35 weeks			
		Total		*HMD*	
Population	*No. of deliveries*	*No.*	*%*	*No.*	*%*
Singletons	11,568	380	3.3	79	20.8
Twins	236	42	17.7	17	40.5

Conclusion

We found that twins with hyaline membrane disease (one or both members of 19 pairs) had significantly lower gestational age, birth weight, and Apgar score, and higher incidence of monozygosity and higher mortality rate than the group without HMD (275 pairs). When both twins were affected (12 pairs), they had lower gestational age and birth weight and increased incidence of monozygosity than when B alone was affected (six pairs). When B was affected alone, he had lower Apgar score than twin A. These findings suggest that: (1) HMD occurs in twins because of lung immaturity, as it does in singletons; (2) the high correlation between monozygotic twins and HMD is probably related to immaturity of these twins; and (3) the higher risk of twin B is probably caused by birth asphyxia as reflected by their lower Apgar scores.

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Serum unconjugated estriol levels in the third trimester and their relationship to gestational age

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Maternal unconjugated estriol levels were measured throughout the 28 to 41 week interval in two groups of accurately dated normal pregnancies. The first group consisted of randomly sampled pregnancies on which 285 unconjugated estriol determinations were performed. The logarithms of the mean values plotted into a positive sloping, relatively straight line which was disrupted by a plateau originating at 31 to 32 weeks and terminated at 35 weeks where there began a steep surge to a point at 36 weeks (surge point) that returned values to fit the previously established straight line. To investigate these findings in individual pregnancies, a second group of nine subjects was studied with serial unconjugated estriol determinations. In all nine of these subjects, the surge point could be identified statistically and occurred at a mean gestational age of 36.0 ± 0.6 (1 S.D.) weeks. Data from the first group of randomly sampled pregnancies indicate that the surge point occurred around a mean gestational age of 36.0 weeks and was confirmed by data from the second group of serially sampled individual subjects showing the surge point as a statistically definable marker in normal pregnancies.

IN NORMAL pregnancy a continued increase in the rate of fetal adrenal growth occurs between 28 and 41 weeks' gestation and becomes particularly marked between 34 and 36 weeks.[1] This is associated with a sharp rise in circulating fetal and amniotic fluid cortisol levels.[2, 3] The exposure of fetal tissues to rising cortisol levels is probably the initiating event in a series of final maturation steps that include increasing pulmonary surfactant production and rising glycogen stores.[4, 5]

The mechanisms controlling fetal adrenal growth and steroidogenesis are largely modulated by the fetal hypothalamus and pituitary.[6–10] Accelerated fetal adrenal growth occurring during the 34 to 36 week interval has been linked to a concomitant rise in levels of circulating fetal pituitary prolactin.[9] In addition, rising cortisol levels are associated with a simultaneous fall (suppression) in circulating fetal pituitary ACTH,[10] implying, as has been demonstrated in sheep, that the fetal adrenal (probably definitive cortex) has become increasingly sensitive to ACTH.[11]

Unconjugated estriol levels, as measured in the peripheral maternal circulation, are known to correlate closely with fetal adrenal steroidogenesis and the fetal corticotrophic mechanisms which regulate it.[7, 8, 12] This consideration led us to study maternal unconjugated estriol levels in a series of uncomplicated pregnancies at carefully documented intervals between 28 and 41 weeks to observe if known changes in fetal adrenal steroidogenesis would be reflected by alterations in maternal serum estriol concentrations.

Materials and methods

Serum unconjugated estriol was measured in a series of normal, carefully dated pregnancies by a specific, rapid, nonchromatographic radioimmunoassay described previously.[13] Serum was obtained by peripheral venipuncture and stored after separation at −20° C. until assayed. Each series of samples was run in the same assay such that between-sample variation was held to < 5.0 per cent. Blood samples were obtained between 13:30 and 15:30 hours from ambulatory outpatients with uncomplicated pregnancies delivering

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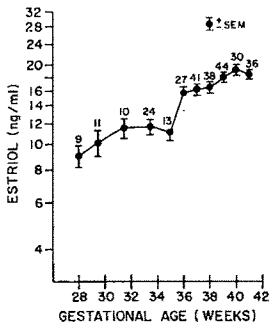


Fig. 1. The means and standard errors for the means from 285 unconjugated estriol determinations between weeks 28 and 41 of gestational age on a semilogarithmic plot. Figures in parentheses indicate the numbers of samples for each point.

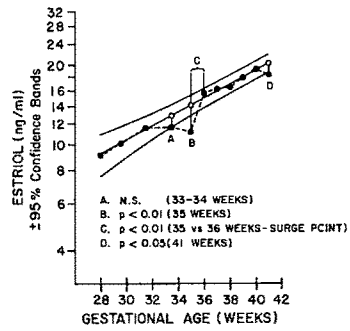


Fig. 2. Logarithmic transformed regression line with 95 per cent confidence limits fitted to points between 28 and 40 weeks with deliberate exclusion of the points at 33 to 34 and 35 weeks where the numbers plateau from the trend of surrounding data points. The 33 to 34 week point *(A)*, and the 35 week point *(B)*, the 35 to 36 week interval *(C)*, and the 41 week point *(D)* are tested statistically for both their relationship to the 95 per cent confidence intervals from the logarithmic transformed regression line and the corresponding values predicted from that line by unpaired t tests.

healthy term neonates. Pregnancies were dated on the basis of accurate and regular menstrual histories, confirmed by accurate midtrimester sizes, and reconfirmed by the pediatrician's examination utilizing standardized published weight, physical, and neurologic criteria.[14–16]

Two groups of pregnant women were studied. The first group consisted of randomly selected subjects from whom one to nine samples were obtained between 28 and 41 weeks' gestation. The great majority were sampled from one to three times for a total of 285 samples. The second group consisted of nine subjects who provided serial samples. Clinical data for these subjects are summarized in Table I.

Data obtained from the first group of subjects were treated in the following manner. The means and standard error of the means from the 285 samples were placed on a logarithmic ordinate plotted against gestational age on a linear abscissa (Fig. 1). The logarithmic transformed mean values plotted into a positive sloping, nearly straight line disrupted by a plateau originating at the 31 to 32 week point and terminating at 35 weeks where a steep surge began and terminated at the 36 week point (surge point) that returned values to fit the previously established straight line. In order to confirm the above impression, a least-squares regression line with 95 per cent confidence limits was placed through all points between 28 and 40 weeks with deliberate exclusion of the 33 to 34 week and 35 week point (Fig. 2). The fit of this line was very close ($r = 0.997$). It was noted that the 33 to 34 week point *(A)* fell exactly on the 95 per cent confidence line and the 35 week *(B)* point well below it, indicating that probably neither point belonged to the straight line logarithmic transformed relationship described above. The 33 to 34 week point *(A)* and the 35 week point *(B)* were then compared by unpaired t tests with corresponding points predicted by the regression line (Fig. 2). For the calculation, it was assumed that corresponding points had the same variance. The difference between points at the 33 to 34 week interval was not significant ($p > 0.05$) but the difference at 35 weeks was highly significant ($p < 0.01$). In order to investigate the significance of the surge point, the mean values and variances for the samples obtained to compute the 35 to 36 week points were compared by unpaired t tests, also confirming a highly significant difference ($p > 0.01$) (Fig. 2). The surge point was also defined another way (Fig. 3). A least-squares regression line was placed through the four points between 29.5 and 35 weeks and extended to week 36 with extrapolation of a future value at 36 weeks ±95 per cent confidence limits of 11.8 ± 1.3 ng per milliliter. The measured level at 35 weeks of 15.3 ng. per milliliter fell

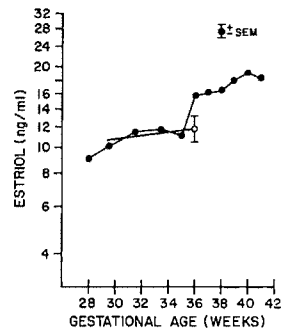


Fig. 3. Statistical definition of the surge point. A least-squares regression line placed through the four points between 29.5 and 35 weeks and extrapolated to week 36 point gives a predicted future value ±95 per cent confidence limits. This first value falling outside of the 95 per cent confidence interval is defined as the surge point.

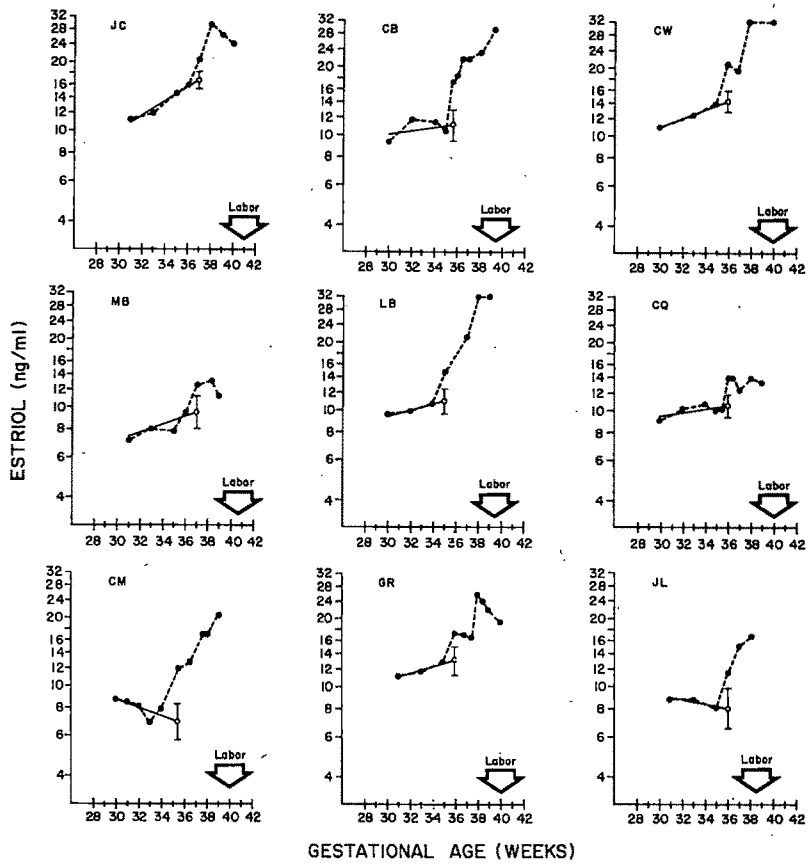


Fig. 4. Individual plots from nine pregnant subjects with accurate dates. The surge point occurs no earlier than 35.0 weeks and no later than 37.0 weeks with a mean of 36.0 ± 0.6 (1 S.D.). In eight of nine subjects labor occurred between 39.5 and 41.0 weeks with a mean surge point to labor interval of 3.9 ± 0.6 (1 S.D.) weeks. In one subject (J. L.), labor occurred at 38.5 weeks with a surge point to labor interval of 2.5 weeks.

well above the 95 per cent confidence interval predicted by the line.[17]

Data from the second group of subjects were treated in the following manner. Individual points were placed on a semilogarithmic plot exactly as described with the mean data from the first group. The surge point was then calculated and defined as follows (Figs. 3 and 4). With the use of the logarithms of the estriol concentrations from the first 3 weeks of observation a least-squares regression line was calculated and plotted. The expected value and its upper 95 per cent confidence limit for the next week's concentration were then calculated from the slope of the line. Whenever the actual observed serum concentration fell below this limit it was assumed to be a part of the previously calculated regression line and a new regression line was calculated incorporating this additional data point. The next actual concentration would then be compared to the predicted next upper 95 per cent confidence limit and the process was continued until the first measured concentration exceeded the upper 95 per cent confidence limit. This point was considered as not part of this regression line and was defined as the surge point.

Results

Data from the first group of pregnancies studied are shown in Fig. 1. This figure depicts the logarithmic means and S.E.M. from 285 serum samples measured for unconjugated estriol levels plotted against the confirmed gestational age in weeks. The over-all positive logarithmic transformed linear slope and the transient downward displacement between 31 to 32 and 35 weeks occur as were noted previously. Although the point at 32 to 33 weeks is not significantly different ($p > 0.05$) from the corresponding value predicted by the regression line, this point falls on the lower 95 per cent confidence band for the entire line, implying that it probably does not belong to the straight logarithmic relationship described by the other points. The point at 33 to 34 weeks appears, therefore, to be transitional since it becomes significant if moved forward another 0.5 weeks ($p < 0.05$).

Table I. Clinical data from nine pregnant subjects selected for sequential studies

Subject	*Age*	*Gravida*	*Para*	*Fetal wt. at delivery (Gm.)*	*Gest. age at delivery (wk.)*	*Apgar (5 min.)*	*Complications*
J. C.	27	4	1	2,948	41.0	9	Cord compression during labor, otherwise none
M. B.	25	1	0	2,693	40.5	9	None
C. B.	24	1	0	3,218	39.5	10	None
L. B.	27	3	2	3,600	39.5	9	None
C. M.	18	2	0	3,303	40.0	9	None
C. Q.	24	2	1	2,562	40.0	10	None
C. W.	25	2	1	3,473	40.0	9	None
G. R.	27	4	3	3,062	40.0	10	None
J. L.	25	3	2	2,736	38.5	9	None

A second decline occurs at 41 weeks. This point falls below an extension of the 95 per cent confidence bands and is also significantly lower ($p < 0.05$) than the value predicted for 41 weeks by the regression line (Fig. 2).

Fig. 3 depicts placement through the mean data points of a least squares regression line as it is used to define the location of the surge point.

Data from the group of nine individual pregnancies studied with serial samples is graphed on individual plots in Fig. 4 and tabulated in Table II. Fig. 4 depicts placements of regression lines, predicted values ±95 per cent confidence intervals, and the placement of the surge point as described. The mean gestational age at which the surge point occurred from all nine subjects was 36.0 ± 0.6 (1 S.D.) weeks. The earliest placement was at 35.0 weeks and the latest was 37.0 weeks. In eight of nine subjects, spontaneous labor occurred between 39.0 and 40.5 weeks, and the mean surge point to labor interval was 3.9 ± 0.6 (1 S.D.) weeks. In one of the nine subjects (J.L.), labor occurred at 38.5 weeks and was associated with a surge point to labor interval of 2.5 weeks.

Table II. Gestational age at time of surge point and surge point to labor interval

Subject	*Gestational age at surge point (wk.)*	*Surge point to labor interval (wk.)*
J. C.	37.0	4.0
M. B.	37.0	3.0
C. B.	35.5	3.5
L. B.	35.0	4.0
C. M.	35.5	4.5
C. Q.	36.0	3.5
C. W.	36.0	4.0
G. R.	36.0	4.5
J. L.	36.0	2.5*
Mean ± 1 S.D.	36.0 ± 0.6	3.9 ± 0.6

*Labor at 38.5 weeks and not included in mean calculation.

Comment

Numerous publications in discussing normal values for serum and urinary estriol during the third trimester have depicted a smooth curve which gradually swings upward until term.[18–21] The 31 to 35 week plateau and 35 to 36 week surge described in this study have so far been unacknowledged. These phenomena may, in part, be unique to the unconjugated fraction of circulating estriol since this moiety is almost exclusively fetoplacental in origin and has not been shifted and metabolized through multiple maternal compartments as are the various estriol conjugates.[22, 23] Another explanation may lie with inaccurate dating of gestational ages in some series. Finally, in several publications the data has been condensed into 2 to 4 week intervals such that the rather short-term events described here would remain unnoticed.[18–21]

Any attempt to explain the downward deviations from an otherwise positive sloping logarithmic transformed line must be speculative with the present state of knowledge. It is plausible that these effects are due to increasing levels of fetal cortisol leading to decreased levels of ACTH.[2, 3, 10] This in turn may cause decreased production of fetal dehydroepiandrosterone sulfate (DHEA-S) with a resultant decrease in placental estriol production.[7, 8] The 35 to 36 week estriol surge is more difficult to explain. The resumption of the previously established upswinging logarithmic transformed linear relationship may represent a sensitizing phenomenon such that the fetal cortex becomes more responsive to fetal ACTH and continues to produce increasing amounts of DHEA-S despite decreased circulating ACTH. Since circulating fetal prolactin rises sharply after week 34 and since it is believed to enhance fetal adrenal growth, lipid biosynthesis, and cholesterol (steroid precursor) storage,[9] it is possible that prolactin may promote increasing fetal adrenal zone sensitivity to ACTH through a permissive or additive effect.

A similar situation may occur in the 40 to 41 week interval where the estriol curve slopes downward. The occurrence may reflect on further increases in fetal cortisol production and additional feedback ACTH sup-

pression just prior to the onset of term labor.[10] In premature labor, an event associated with rising maternal estradiol levels and falling progesterone levels,[24] estriol concentrations have not been studied. However, the changes observed in estriol concentrations at around 36 weeks may be more related to the steriod mediated maturation process active at that time rather than to the mechanisms triggering the onset of labor, as suggested by the findings in subject J. L., who labored at 38.5 weeks, 2.5 weeks after the estriol surge point.

Determination of the surge point in individual pregnancies could be utilized as a noninvasive clinical test for dealing with patients who are first encountered during the third trimester and are complicated by inaccurate or misleading dates. The multitude of irritating, as well as frankly hazardous, problems associated with "bad date" pregnancies are well known to all practicing obstetricians. These data indicate that, in a normal pregnancy destined to deliver at term, determination of the surge point would permit: (1) an accurate estimation of the term parturition date without other clinical information and (2) indicate the time at which adrenal steroidogenesis has already been shifted toward increasing corticoid production and, by inference, increasing pulmonary surfactant production. This latter point will clearly require further documentation.

In order to utilize the surge point determination for clinical purposes, it is essential that all samples be run through the same assay in adjacent tubes so as to minimize methodologic errors. It is, therefore, our current practice to "bank" weekly blood samples from patients with poor dates with the expectation of running the entire series if the need should arise. The calculation is best carried out with four or more points in which to place a regression line. If three points are utilized, the regression line must fit very closely in order to predict a future value with a workably narrow 95 per cent confidence interval. Preliminary clinical experience with this approach has been encouraging.

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GYNECOLOGY

The use of prereduced media and a portable jar for the collection of anaerobic organisms from clinical sites of infection

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A system for the isolation of anaerobic organisms from clinical specimens was evaluated at the LAC-USC Medical Center. Clinicians were provided with a Gas Pak with a broth tube and two prereduced blood plates for direct inoculation of specimens. In the first 50 patients evaluated, 74 separate anaerobic isolates were recovered in 36 patients, 72 per cent of the total. Bacteroides fragilis *was the most common organism recovered. The impact of this system upon clinical management is discussed.*

A NUMBER of recent studies have shown that anaerobic organisms can be recovered from the majority of soft tissue pelvic infections.[1, 2] This 70 per cent or greater recovery rate of anaerobes has been achieved by the use of oxygen-free tubes for the transport of specimens to the laboratory, to diminish specimen exposure to oxygen. In the laboratory, primary plating and anaerobic inoculation are carried out. A major problem for the obstetrician-gynecologist is the frequent clinical recognition of serious soft tissue pelvic infections during evening and early morning hours when laboratory personnel may not be available for the tasks of primary specimen plating and anaerobic incubation.

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To permit these laboratory procedures to be performed at the bedside by the physician, an alternate system of specimen collection has been evaluated at the Los Angeles County–University of Southern California (LAC-USC) Medical Center. This system utilized plates of prereduced media and broth in a Gas Pak* jar, with physicians performing the inoculation and streaking of specimens. This was followed by immediate activation of the Gas Pak system, and placement in an incubator. It is the purpose of this paper to present our results with this system, in the first 50 patients from whom purulent material was directly recovered from soft tissue pelvic infections.

Materials and methods

These 50 consecutive purulent specimens were obtained from a variety of infection sites. The majority were gathered from material excised or drained in the

*Gas Pak, BBL, a Division of Becton, Dickinson and Company, Cockeysville, Maryland.

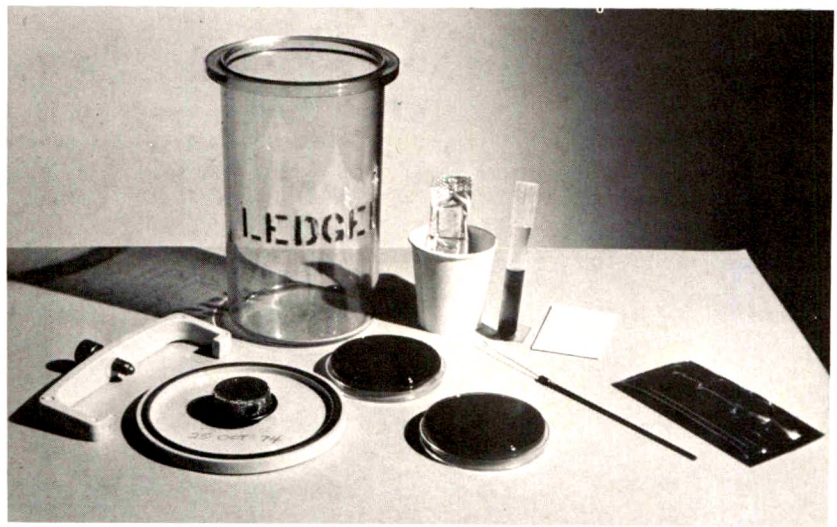


Fig. 1. The Gas Pak system provided for clinicians. It includes three collection units, thioglycollate broth with bactofildes added, a plain blood agar plate, and a blood agar plate with vancomycin and kanamycin added. In addition, there is a wire loop for streaking of the plates, an indicator strip, and a packet for the generation of carbon dioxide and hydrogen.

operating room. The remainder of the purulent specimens were obtained by direct needle aspiration of a Bartholin's abscess or direct specimen collection from a purulent wound.

The specimens were inoculated in three separate media systems: a tube of thioglycollate broth with Bactofildes added, a sheep blood agar plate, and a sheep blood agar plate with vancomycin and kanamycin added (see Fig. 1). These three media systems had been prereduced in an activated anaerobic Gas Pak for at least 24 hours prior to use. All three culture systems were inoculated. With a wire loop, each of the two agar plates was streaked. The plates and thioglycollate tube were then returned to the Gas Pak jar, which was sealed, activated, and placed in an incubator to be collected by laboratory personnel during daylight hours.

The following confirmation tests were performed on the anaerobic isolates. Peptostreptococci and peptococci were classified on the basis of cellular morphology from distinct colonies. Gram-positive bacilli were classified on the basis of being spore formers or not. Spore-forming anaerobic gram-positive bacilli were identified only as *Clostridium* species, except that *perfringens* was specifically identified by a series of biochemical tests including demonstration of alpha toxin. Gram-negative organisms were tentatively identified on the basis of antibiotic disc susceptibilities proposed by Sutter and Finegold.[3] All anaerobic isolates were subjected to antibiotic disc susceptibility testing, by the method of Sutter.[4]

Results

The primary sites of infection are noted in Table I. During this time interval of study, most of the specimens were collected in the operating room.

Anaerobic bacteria were recovered from 36 of the 50 specimens (72 per cent). The number of anaerobic isolates in an individual specimen varied from one to five. The frequency of the anaerobic isolates is noted in Table II. In these 36 positive specimens, anaerobes were isolated 74 times, as noted in Table III. *Bacteroides fragilis* was the most common anaerobe isolated from soft tissue infection sites. Table IV documents the recovery of anaerobic isolates by the various media used.

An additional analysis of the anaerobic data was based on the preoperative exposure of part of this patient population to antibiotics prior to obtaining specimens for culture. As shown in Table V, the preoperative administration of antibiotics did not alter the frequency of anaerobic isolations. The differences noted are not statistically significant. A further analysis of preoperative antibiotic use is noted in Table VI. The numbers of observations are small, but the data is suggestive that preoperative use of antibiotics other than clindamycin or chloramphenicol may create a more favorable environment for anaerobes. The data were further analyzed to determine the impact of the duration of preoperative use of clindamycin or chloramphenicol upon the isolation of anaerobes. This is pictured in Fig. 2. The difference between anaerobic isolation between the two groups is highly significant according to the Fisher exact test ($p < 0.01$).

Table I. Culture source of purulent material

	Total
1. Free pus in peritoneal cavity at laporatomy	18
a. Salpingo-oophoritis (8)	
b. Post-cesarean section infection (6)	
c. Pelvic malignancy (2)	
d. Appendiceal abscess (2)	
2. Tubo-ovarian abscess	17
3. Culpotomy drainage of pelvic abscess	4
a. Post-cesarean section infection (2)	
b. Salpingo-oophoritis (2)	
4. Abdominal wound abscess	3
5. Postoperative ovarian abscess	2
6. Amnionitis	2
7. Pyometra	1
8. Postoperative vaginal cuff collection	1
9. Abdominal wall abscess	1
10. Bartholin's abscess	1
	50

Table II. Number of anaerobes isolated

	No.
One anaerobe	13
Two anaerobes	12
Three anaerobes	8
Four anaerobes	2
Five anaerobes	1

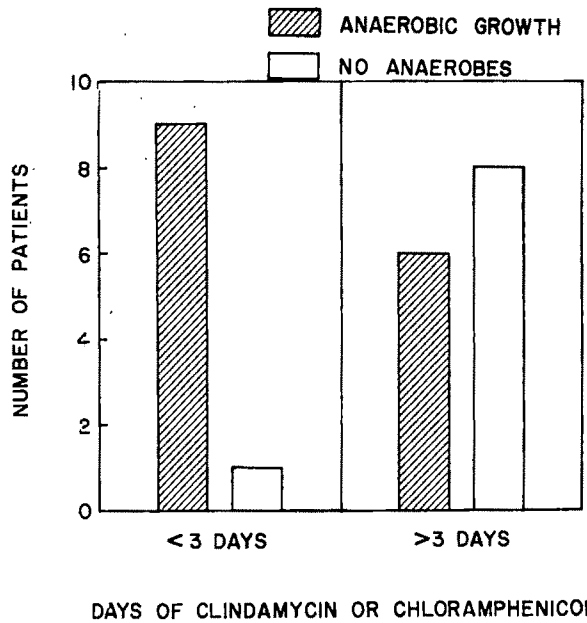


Fig. 2. The isolation of anaerobes from abscesses, depending upon the length of preoperative exposure to clindamycin or chloramphenicol. There is a significant increase in the recovery of anaerobes when the preoperative duration of therapy is 3 days or less. $P < 0.01$ by the Fisher exact test.

Comment

This system for anaerobic organism recovery was successful in our clinical and laboratory setting. The blood agar plates probably require 10^3 bacteria or more per milliliter for surface survival and growth on the plates.[5] The applicability of these prereduced plates in the recovery of anaerobes from soft tissue infections is reflected by the recovery of 66 of 74 anaerobic isolates (89 per cent) from plates (see Table IV). This is in contrast to a recent study of vaginal surface bacteria from this institution using the same Gas Pak system, in which only 51 of 130 anaerobic isolates (39 per cent) were recovered from primary plating.[6] These differences are statistically significant: chi-square equals 45.75 with a P value of less than 0.001. This variation reflects the differences in the quantities of anaerobic bacteria in the inoculum, with larger numbers of bacteria present in an abscess than on a previously cleansed and prepared vaginal mucosal surface. By plating the samples directly, without enrichment in a broth culture, earlier microbiologic information was available for the physician as the appearance of some colonies and their gram-stained smears were characteristic enough to permit a preliminary report of the presence of anaerobes, usually within 48 hours of the initial inoculation of the specimen. This will permit better therapeutic decisions, particularly in the patient who remains febrile despite antibiotic therapy. In the current use of the Gas Pak for patients with serious soft tissue pelvic infections, the thioglycollate tube provides a safety factor in case the jar provides faulty anaerobiasis because of defective carbon dioxide and hydrogen generating packs, a faulty seal, or failure of the catalyst pellets. The eight isolates, recovered only from the thioglycollate, were not those associated with serious infections. In our laboratory, the pallidium pellets are reactivated by heating at 160° F. for 2 hours after each use, in an attempt to increase the efficiency of the Gas Pak system.

In our clinical setting, this culture technique has become a standard procedure. No system requiring direct inoculation and plating by physicians can work unless there is some prior educational effort. The major impetus for success comes from the feedback to the physician of rapid isolation and identification of anaerobes. These anaerobic isolations replaced the former "no growth" reports and had an impact upon the clinical care of many of these women prior to discharge. With each passing month, a marked improvement in physician plating techniques was seen.

This method for anaerobic isolation compares favorably with other methods recently reported in our literature. The percentage of anaerobic recovery in previously reported studies ranges from 20 to 40 per

Table III. Anaerobes isolated

I. Gram-positive		II. Gram-negative	
A. Cocci		A. Cocci	
1. Peptococci	17		
2. Peptostreptococci	11		
B. Bacilli		B. Rods	
1. Spore formers		1. *Bacteroides fragilis*	18
a. *Clostridium perfringens*	2	2. Bacteroides species	5
b. Clostridium species	2	3. Rods, not identified	3
2. Non–spore formers		4. Fusobacterium	1
a. Bacilli, not identified	14		
b. *Propionibacterium acnes*	1		
Total	47		27

Table IV. Isolation of anaerobic species

	No.
Thioglycollate broth only	8
Plain sheep blood agar plate only	46
Vancomycin-kanamycin plate only	4
Both plain blood agar and V-K plates	16
	74

Table V. Anaerobic recovery based upon the patients' preoperative exposure to antibiotics

	No antibiotics	*Antibiotics*	*Total*
No anaerobes	5	9	14
Anaerobes	11 (69%)	25 (76%)	36 (72%)
Total	16	34	50

cent with transport media[7] to 74[2] and 100 per cent[1] with oxygen-free tubes and primary plating with anaerobic incubation in the laboratory. Although our study was not a prospective comparison study with older methods using transport media, the 72 per cent recovery of anaerobes is many-fold greater than the previous recovery of anaerobes from abscesses in this institution. A recent survey of bacteremia from the LAC-USC Medical Center covering a 1 year period beginning in August, 1972, prior to the institution of primary anaerobic plating, showed that the agreement between positive blood cultures and recovery of the same organism from cultures of the primary infection site was greatest when aerobic bacteria were isolated from the blood.[8] There was no parallel recovery of anaerobes from the primary site of infection, because of inadequate anaerobic methodology. This suggests the relative insensitivity of previous techniques for isolating anaerobes from soft tissue infection sites.

Because of the ability of this sytem to recover anaerobes, a critical factor in its clinical employment is the care necessary for specimen collection. The 70 per cent recovery of anaerobes from the surface of previously prepared vaginal tissue, at the completion of a vaginal hysterectomy, gives some sense of the mucous membrane presence of these organisms. Direct needle aspiration or collection of infected material is necessary. Because of this, we have abandoned the endocervical approach for anaerobic analysis of patients with suspected salpingo-oophoritis or a postpartum endomyometritis. Alternate routes for culture will be the subject of future reports from this institution.

The identification of specific species of anaerobes in this study represents incomplete methods. More sophisticated systems, utilizing gas chromatography, provide more precise identification of anaerobes, so that the microbiologic data are reproducible and meaningful, However, at the present level of laboratory development of capabilities in the LAC-USC Medical Center, the Gas Pak system provides physicians with two important aids in their evaluation of patients. First, anaerobes can be isolated from soft tissue sites of infection, in percentages comparable to a more sophisticated system. Second, rapid information can be transmitted to the physician indicating that anaerobic gram-negative rods are a distinct possibility, so that appropriate antibiotic coverage for *Bacteroides fragilis* can be considered. More detailed techniques of identification are the goals of our laboratory, but the time delay in the final report suggests to us that the acquisition of this capability will have little impact on the clinical care of these seriously ill patients.

Another possible factor in the recovery of anaerobic organisms from soft tissue infection sites is prior patient exposure to antibiotics. At the time of specimen collection in previous studies of soft tissue pelvic infections in women, either the patients had no prior exposure to clindamycin or chloramphenicol[1] or prior exposure to any antibiotics was limited to 24 hours or less.[2] In the present study, we could demonstrate no difference in the recovery of anaerobic organisms comparing patients who had no prior antibiotics to those who had received any antibiotics or

Table VI. Anaerobic recovery based upon the patients' preoperative exposure to antibiotics, especially clindamycin or chloramphenicol

	No antibiotics	*Antibiotics, but no clindamycin nor chloramphenicol*	*Clindamycin or chloramphenicol*	*Total*
No anaerobes	5	0	9	14
Anaerobes	11 (69%)	10 (100%)	15 (63%)	36 (72%)
Total	16	10	24	50

specifically either clindamycin or chloramphenicol (see Tables V and VI). Of great interest to us was the heavy recovery of anaerobes in patients with prior exposure to antibiotics other than clindamycin or chloramphenicol. If these findings are confirmed in future studies of soft tissue pelvic infections in obstetrics-gynecology, this should have an impact upon antibiotic prescription patterns.

These microbiologic observations are limited in number but they suggest important clinical implications. The frequent recovery of more than one anaerobe, and the frequent isolation of *Bacteroides fragilis* from pelvic soft tissue abscesses suggest that clindamycin or chloramphenicol should be part of the treatment regimen in patients suspected of having this problem on clinical grounds. The striking drop in the recovery of anaerobes from soft tissue infection sites when patients had more than 3 days of clindamycin or chloramphenicol therapy (see Fig. 2) is an intriguing laboratory observation. A constant clinical question, particularly in the treatment of hospitalized patients with recurrent salpingo-oophritis, is the appropriate time interval for a clinical trial of antibiotics before operative intervention is considered necessary for the cure of a pelvic infection. In view of these microbiologic data, it would appear that a minimum of three days exposure to clindamycin or chloramphenicol is needed before one would expect elimination of anaerobes. Any prior clinical judgment of a therapeutic failure would be premature. In addition, the frequent recovery of more than one anaerobe indicates the mixed nature of many of these soft tissue infections. Prospective comparative studies are needed to determine the appropriate choice of antibiotics in these women.

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The influence of copper on the in vitro motility of the human Fallopian tube

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Experiments were designed to examine whether one contraceptive action of the copper intrauterine contraceptive devices (Cu-IUD's) could be associated with an influence on the smooth muscle activity of the Fallopian tube. Sections of the isthmic portion of human oviducts were removed during operation. Preparations from the circular muscle layer were mounted for isometric recording of contractile activity. Subsequently, spontaneous rhythmic contractions appeared within one to five minutes after the preparation procedure was completed. Transmural nerve stimulation or addition of norepinephrine or prostaglandin $F_{2\alpha}$ to the Tris buffer medium caused an increase in tone and frequency. Addition of $CuCl_2$ caused a concentration-dependent increase in frequency and a concomitant decrease in amplitude. High concentrations of $CuCl_2$ produced a marked initial increase in frequency, but the rhythmic activity was soon abolished. Metallic copper in the incubation medium caused the same qualitative effects on the smooth muscle preparation as $CuCl_2$. Influences of copper on contractions of rat portal vein preparations were studied in the same way, and similar effects were found. The copper concentration of the secretion in the Fallopian tube was measured by atomic absorption in seven patients wearing CU-IUD's until operation. The levels found were of the same order of magnitude as the concentration of free copper ions which in vitro caused effects on the smooth muscle. It is concluded that copper can affect smooth muscle activity. An influence of copper on the motility of the human oviduct has to be considered as a possible factor contributing to the contraceptive action of the Cu-IUD.

COPPER INTRAUTERINE contraceptive devices (Cu-IUD) have become widely used since their introduction, but their specific contraceptive action is far from clear. Copper has been demonstrated to impair implantation by influencing enzymatic activities in the human endometrium.[5] Under experimental conditions, copper has been found to be lethal to the mouse blastocyst[2] and to reduce motility of human spermatozoa.[7]

Another possible contraceptive mechanism of copper, investigated in the present study, is an interference with the motility of the human Fallopian tube. The physiologic regulation of the oviduct is complex. In experiments on various animal models and on the human Fallopian tube, estrogens, in general, have been found to increase rate, amplitude, and tone of the spontaneous tubal contractions.[16] During specific phases of the menstrual cycle, progesterone exerts the opposite effect.[18] Prostaglandins (PG's) of the E type induce contractions in the segments next to the uterus with concomitant relaxation in the rest of the tube,[22] while PG's of the F type cause contractions in the whole Fallopian tube.[20]

In the present study, a method was developed for direct analysis of the copper influence on isolated preparations of the smooth muscle of the human Fallopian tube. The tissues were obtained from patients undergoing operation for hysterectomy or sterilization. The time of operation was chosen to correlate with the early secretory phase of the menstrual cycle. The influence of copper was also

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studied in another smooth muscle preparation—the rat portal vein—with similar experimental conditions.

Material and methods

Subjects. The study included 18 women with normal cycles (25 to 35 days) who were admitted for hysterectomy or sterilization. The indications for operation were predominantly myomas or menorrhagia. Ten were between 40 and 46 years old, and eight were younger (range 30 to 40 years of age). Only one was nulliparous. In five, a Cu-IUD (Cu-7-200*) had been inserted 1 to 6 weeks prior to operation. Fifteen women were in the secretory phase, i.e., 16 to 24 days after the last menstrual period. Endometrial biopsies in these women were early luteal or midluteal, plasma progesterone levels were between 11.5 and 15.0 ng. per milliliter, and new corpora lutea were seen. Three women were considered to be in the pre- or periovulatory phase. In these, the endometrial biopsies were proliferative, plasma progesterone levels were between 1.0 and 1.2 ng. per milliliter, and there were no convincing signs of new corpora lutea. The size of the uterus, measured by a sound, varied between 70 and 120 mm. Premedication was meperidine hydrochloride, 50 mg., promethazine chloride, 25 mg., and atropine sulfate, 0.5 mg., given intramuscularly one hour before operation. General anesthesia was induced with hexobarbital sodium and succinylcholine chloride and maintained with nitrous oxide and oxygen, combined with intermittent injections of meperidine hydrochloride and diallyl-bis-nortoxiferine dichloride.

Collection of tubal secretion. In all patients baby-feeding catheters were inserted into the Fallopian tubes bilaterally and distally immediately after the abdomen was opened. By means of a syringe, the luminal fluid was gently drawn into the catheters. Samples contaminated with blood were rejected. Copper analyses were then performed as described below. In the first few experiments, the samples were stored frozen until analyzed, and many of these secretions then could not be removed from the catheters when thawed. However, the majority of the samples were not frozen but were kept in a refrigerator until analyzed, normally the same day.

Organ bath experiments. A section, 10 mm. in length, was carefully removed from each Fallopian tube approximately 10 mm. from the uterine tubal junction. The specimens were immediately placed in oxygenated and chilled Tris-buffer salt solution, composition as described below. The time interval between

*Gravigard, G. D. Searle & Co.

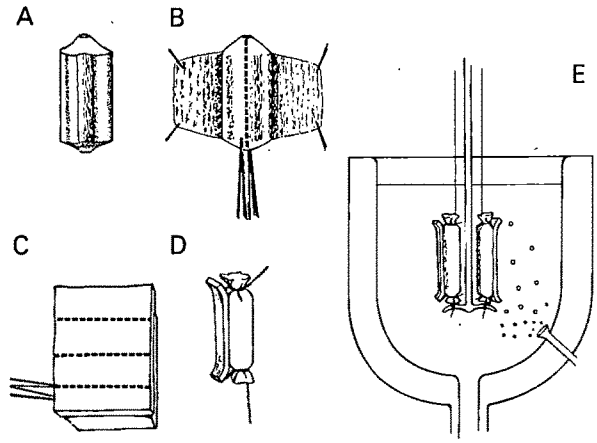


Fig. 1. Schematic illustration of the method for isolation of the circular smooth muscle of the human Fallopian tube *(A to D)* and the mounting of two preparations in an organ bath for isometric recording of smooth muscle activity *(E)*.

start of operation and removal of the Fallopian tube segments did not exceed 15 minutes, and the period of warm ischemia was less than 30 seconds. In the laboratory, tissues surrounding the circular smooth muscle layer of the oviduct were removed under a dissecting microscope (Fig. 1, *A*). The specimen was then opened longitudinally by scissors (Fig. 1, *B*) so that a rectangular sheet was obtained, one surface of which was covered by mucosa. The latter was removed only at the margins in order not to damage the muscle. The actual preparations were then obtained by cutting the tissue in the direction of the circular muscle fiber, i.e., perpendicular to the length axis of the Fallopian tube (Fig. 1, *C*). The specimens measured approximately 5 mm. in length and weighed 10 to 15 mg. (wet weight) which corresponds to a cross-sectional area of 2 to 3 sq. mm. The specimens were tied at each end under the microscope, and inclusion of the mucosa in the silk ligatures was avoided (Fig. 1, *D*). They were attached at one end to a tissue holder in a mantled 30 ml. organ bath (37° C.) with Tris-buffer solution (see below). The other end of the tissue was attached to a force transducer* under a passive force of 200 to 300 dynes for isometric recording of contractile activity on a polygraph.† In order to quantitate the phasic activity, the force signal was electronically integrated so that deflections proportional to the mean force during each minute were also obtained on the polygraph. The mounting of the tissue was normally completed within one hour after removal from the patient. Other

*FT.03, Grass Instrument Co., 101 Old Colony Ave., Quincy, Massachusetts 02169.

†Grass Instrument Co.

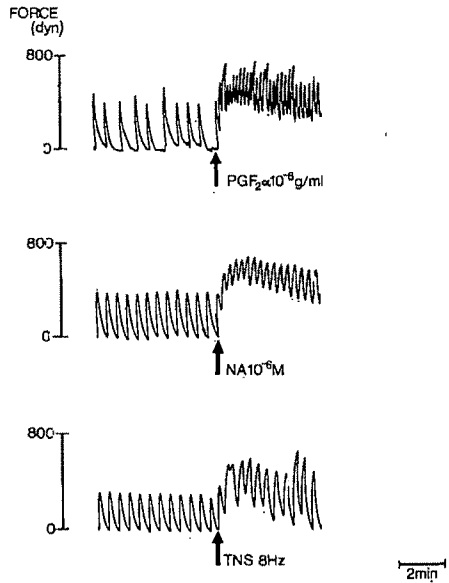


Fig. 2. Isometric recordings of spontaneous activity of the human Fallopian tube in vitro (control periods) and of induced responses to $PGF_{2\alpha}$, norepinephrine *(NA)*, and transmural electrical field stimulation *(TNS)*.

preparations dissected at the same time were stored in cold, oxygenated buffer solution for experiments later during the same day. Thus, 10 to 12 preparations could be studied from the two 10 mm. segments of the isthmic portion of the Fallopian tubes of each patient.

The rat portal vein. A smooth muscle preparation, frequently used in our laboratory, was studied in a separate set of experiments. The isolation and mounting procedures of this muscle have been reported earlier.[13] In some experiments the preparations were placed between platinum electrodes for selective activation of the nerve supply by transmural field stimulation with graded (1 to 64 Hz) frequencies (0.4 msec., 15 v.).[8]

Buffer. The buffer consisted of: NaCl, 135 mM; KCl, 6 mM., $MgCl_2$, 2.5 mM.; $CaCl_2$, 2.5 mM.; tris(hydroxymethyl)aminomethane, 15 mM.; D-glucose, 5 mM. The buffer (300 mOsm.) was titrated against hydrochloric acid at 37° C. to give a pH of 7.4. It was constantly bubbled with 100 per cent oxygen throughout the incubations.

Chemicals: $CuCl_2$, grade A; prostaglandin $F_{2\alpha}$* ($PGF_{2\alpha}$); and norepinephrine† were dissolved to proper concentrations prior to each experiment. The IUD used was the Cu-7-200.

Copper analysis. A graphite tube furnace for flameless atomic absorption spectroscopy was used for the analysis of the content of copper in incubation media, serum, and secretions of the human oviducts.[24]

Statistics. Mean values and standard errors of the means (S.E.'s) were calculated according to conventional statistical methods. Differences between mean values were tested by Student's t test and were considered significant at $p < 0.05$.

Results

Activity of the human Fallopian tube. After the smooth muscle preparation had been mounted in the organ bath, a spontaneous phasic mechanical activity normally appeared within a few minutes. The contractile pattern, which stabilized during the one hour accommodation period, was characterized by intermittent rhythmic contractions at a frequency of one to four per minute (see control periods of Figs. 2 and 3). Different preparations from one particular oviduct and often from both tubes of one patient displayed strikingly similar patterns of spontaneous activity. However, variations often occurred between patients with regard to frequency and particularly to amplitude of contraction (200 to 1,000 dynes). These differences could not be directly correlated to the phase of the menstrual cycle in this small number of subjects (see "Material and methods" section). The excitatory influence of exogenous $PGF_{2\alpha}$ norepinephrine, and transmural nerve stimulation (TNS), respectively, is illustrated in Fig. 2. In response to such stimuli, a tetanus-like activity, characterized by increased rate and amplitude of contractions, ensued. The excitatory effects of norepinephrine and TNS varied among the preparations, and the induced responses often declined despite continued exposure. They could be abolished by the α-adrenergic blocking agent phenoxybenzamine (10^{-6}M). After such blockade, norepinephrine and NS were sometimes found to cause reduction of the spontaneous activity which could be antagonized by propranolol (10^{-6}M).

In the initial experiments, $PGF_{2\alpha}$ was always found to give pronounced excitatory responses (Fig. 2, upper recording), which were more easily reproducible than those obtained with norepinephrine at repeated exposures. Furthermore, the excitatory influence was well maintained during the three-minute exposure periods. For these reasons, $PGF_{2\alpha}$ (10^{-6} Gm. per milliliter) was routinely administered as an initial reference response.

In one set of experiments, the influence of $CuCl_2$ in graded concentrations was investigated. Smooth muscle preparations from eight different patients, all in the secretory phase, were tested. The pattern illustrated in Fig. 3 was consistently found. Administration of $CuCl_2$

*The Upjohn Co., 7171 Portage Rd., Kalamazoo, Michigan 49001.

†Nor-Exadrin, Astra Ltd., Sweden.

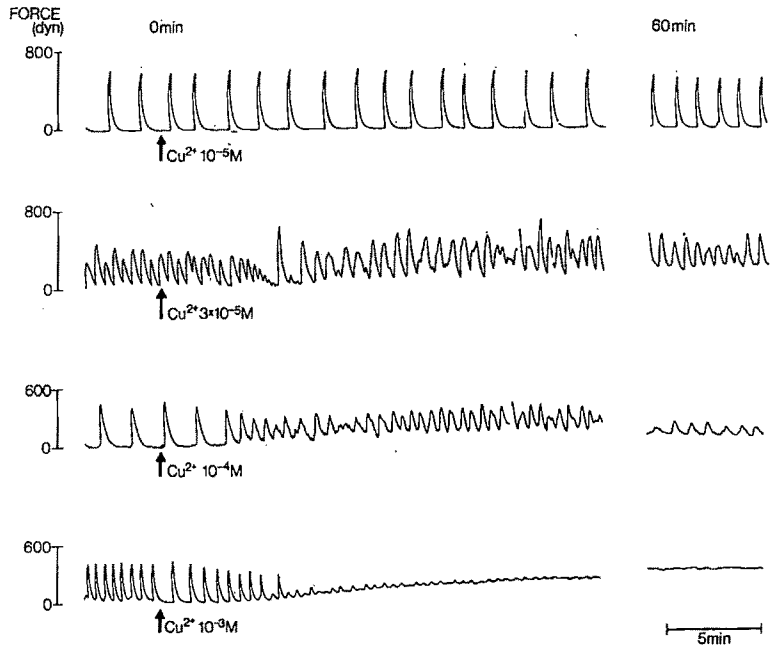


Fig. 3. Effects of $CuCl_2$ in graded concentrations on the spontaneous phasic activity of four smooth muscle preparations of the human Fallopian tube. The copper salt was injected at the arrows. Recordings at right show the activity 60 minutes later. Note induced elevation of base-line tension, decrease in amplitude, and increase in frequency of phasic contractions.

in a concentration of 10^{-5}M (Fig. 3, top) had little influence on the spontaneous activity during the 60 minute exposure period. As the concentration was raised threefold, a tendency toward an increase in frequency of contractions was most often noted within 15 to 20 minutes, and the phasic activity no longer returned to the same base line after 60 minutes of exposure. $CuCl_2$ in a concentration of 10^{-4}M always caused a clear-cut increase in frequency within five to 10 minutes and a gradually decreasing contraction amplitude with concomitant elevation of the base line. Phasic activity was still obtained after 60 minutes but eventually faded away. Administration of $CuCl_2$ in the highest concentration tested, 10^{-3}M (Fig. 3, bottom), also led to an initial increase in frequency and a decrease in amplitude, but the rhythmic contractions disappeared within 15 minutes. The tonic increase in force, also clearly seen after one hour of exposure to 10^{-3}M $CuCl_2$, gradually declined in the course of the next few hours.

In another series of experiments, the effects of metallic copper introduced into the Tris-buffer solution were studied. Tracings from one representative experiment are shown in Fig. 4. The copper wire with a surface area of 200 sq. mm. was placed in the bath fluid (30 ml.) after a stabilizing period. In another organ bath, two preparations from the same segment of the oviduct were placed in normal Tris buffer to serve as controls throughout the experiment (Fig. 4, lower recording). The pattern of spontaneous activity was initially similar in the two tracings illustrated (Fig. 4, panel at time *0 h*). In the control preparation, the contraction amplitude remained unchanged, and regular phasic activity was recorded throughout the experiment. The influence of the metallic copper on the test preparation is apparent from the upper set of recordings of Fig. 4. After only 30 minutes, a clear-cut increase in frequency was recorded. One hour after the introduction of the copper wire, the phasic activity no longer relaxed to the initial base line, and, 30 minutes later, only an erratic activity of low amplitude remained at an increased force level. All phasic activity eventually disappeared after two and one-half hours leaving the tonic increase in force. The copper concentration of the buffer solution was measured at 30 minute intervals. The resulting concentration values (micromolar) are shown in Fig. 4. A comparison between the activity patterns shown in Fig. 3 and Fig. 4 demonstrates that corresponding concentrations of copper give rise to the same qualitative effects whether graded concentrations of $CuCl_2$ are administered or a copper wire is the source of the metal ions present in the buffer.

It is worth noting that the ratio between the concentration producing the maximal response and the threshold level is quite small. As seen in Fig. 3, a

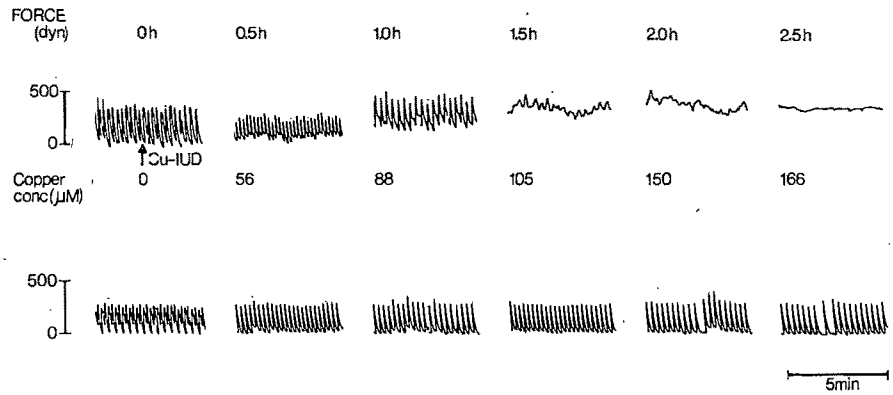


Fig. 4. Effects of metallic copper on the activity of the human Fallopian tube preparation (upper series of tracings). A copper wire (200 sq. mm. surface area) was introduced into the 30 ml. bath at the arrow. Each subsequent tracing shows mechanical activity at 30 minute intervals for 5 minutes. Measured copper concentrations (micromolar) given below. The lower series of recordings represent spontaneous activity of a control preparation from the same Fallopian tube studied simultaneously in a separate experiment. Note that the rate of contraction tends to increase within 0.5 hours, the base line becomes elevated within 1 hour, and the amplitude of contractions decreases within 1.5 hour as a consequence of dissolved copper.

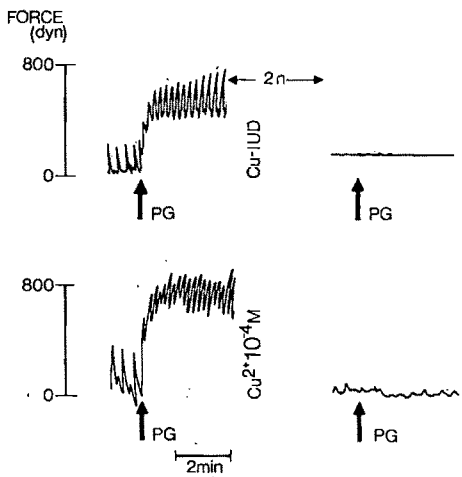


Fig. 5. Elimination of spontaneous activity and excitatory responses to $PGF_{2\alpha}$ *(PG)*, 10^{-6} Gm. per milliliter, after exposure to a metallic copper wire with a 200 sq. mm. surface area *(Cu-IUD)* (upper recording) and $CuCl_2$, $10^{-4}M$ (lower recording), respectively, for 2 hours.

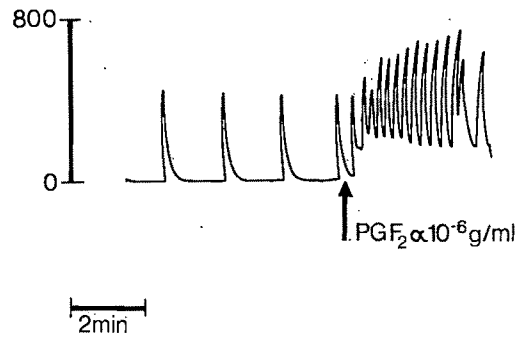


Fig. 6. Spontaneous activity and response to prostaglandin $F_{2\alpha}$ of isolated smooth muscle preparation from patient who had worn a CuIUD for four weeks prior to the experiment.

$CuCl_2$ solution at a concentration of $10^{-5}M$ did not noticeably interfere with the muscle activity, whereas a tenfold higher concentration abolished all spontaneous contractions.

After extinguishing the spontaneous rhythmic activity by copper, the responsiveness of the smooth muscle preparation was tested by administration of $PGF_{2\alpha}$ as illustrated in Fig. 5. In the left panel, recordings of control responses to $PGF_{2\alpha}$ (10^{-6} Gm. per milliliter) are seen. After repeated rinsing of the bath, the spontaneous activity returned to the initial level within approximately five minutes. The muscle was then exposed to $CuCl_2$ ($10^{-4}M$) (upper recording) or to metallic copper (200 sq. mm. surface area) (lower recording). After two hours, there was no spontaneous activity in either of the preparations. In the control preparation, however, the spontaneous activity remained essentially unchanged during this period of time (see Fig. 4). Addition of $PGF_{2\alpha}$ to the muscles exposed to copper for two hours did not lead to any response (Fig. 5, right panel). In preparations where the rhythmic activity had ceased because of copper exposure, neither spontaneous activity nor any response to excitatory influences ($PGF_{2\alpha}$, norepinephrine, or TNS) could, in fact, be re-established even when repeated washings with fresh Tris buffer were made.

Seven patients had worn a Cu-7-200 IUD for one to six weeks prior to the operation. The smooth muscle from the Fallopian tubes of one of these patients,

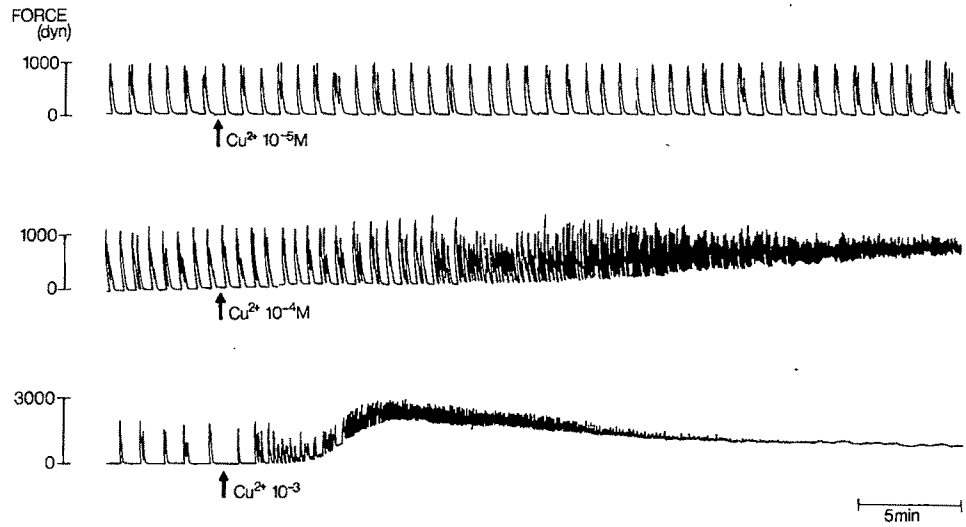


Fig. 7. Spontaneous activity of three preparations of the rat portal vein (control periods) and responses to $CuCl_2$ in graded concentrations, injected at arrows

studied early during the series of experiments, did not show spontaneous activity and responded only weakly to excitatory influences. It is probable that this was due to technical difficulties during the experiment. The isolated preparations of the Fallopian tubes from the other six patients displayed apparently normal spontaneous activity in the organ bath experiments and responded to $PGF_{2\alpha}$ (Fig. 6).

Copper concentrations in tubal secretions. The values obtained for copper concentration in the tubal secretions of patients with and without a copper IUD were 30.7 ± 14.2 μM (No. = 4) and 16.5 ± 4.6 μM (No. = 9), respectively; the values thus were doubled in patients with the copper IUD. The large variation in the group with copper IUD's appeared to be inversely related to time between insertion of the IUD and the operation (one to six weeks).

Activity of rat portal vein. In a separate set of experiments, the effects of $CuCl_2$ were also examined on the longitudinal smooth muscle of the rat portal vein. This preparation displays spontaneous activity (Fig. 7) of a pattern similar to that found in the human Fallopian tube in vitro. As illustrated in Fig. 7, three different concentrations of $CuCl_2$ added to the Tris-buffer solution caused qualitatively similar effects of the portal vein activity as compared to those found in the isolated preparations of the human oviduct (Fig. 3). For practical reasons, the rat portal vein was better suited for quantitative analysis of the $CuCl_2$ influence than was the human smooth muscle (see the "Comment" section). The activity during a control period of five minutes and during the consecutive 180 minutes after administration of $CuCl_2$ was quantitated (see "Material and methods") and expressed as a percentage of the mean control activity. In Fig. 8, mean response values ± S.E. (No. = 4) are shown. It is seen that the force development did not increase during a 30 minute period of exposure to 10^{-5}M $CuCl_2$, whereas a significant ($p < 0.001$) response developed within five minutes after the administration of 10^{-4}M $CuCl_2$. The tenfold higher concentration caused a much more pronounced increase ($p < 0.001$) in mean force within 10 minutes than did 10^{-4}M $CuCl_2$ (Fig. 8).

Comment

After isolation of the circular smooth muscle of the Fallopian tube, the specimens began to contract spontaneously in the organ bath within a few minutes, and excitatory responses could readily be obtained. In earlier investigations on the Fallopian tube, studied during the secretory phase, norepinephrine has been shown to increase both tonic and phasic activity of the longitudinal muscle in vitro[21] and contractility of the whole muscular wall in vivo.[3] Such effects were also obtained in the present muscle preparation and could be attributed to α-adrenergic receptor stimulation. Nerve-induced responses (see Fig. 2, lower panel) were apparently mediated via adrenergic fibers.[3] No attempt was made to assess the role of cholinergic nerves since the patients had been treated with atropine. As mentioned in the introduction, prostaglandins of the F type have a stimulatory effect upon the longitudinal muscle layer in vitro[20] and on tubal motility in vivo.[4] A stable response could always be induced by $PGF_{2\alpha}$

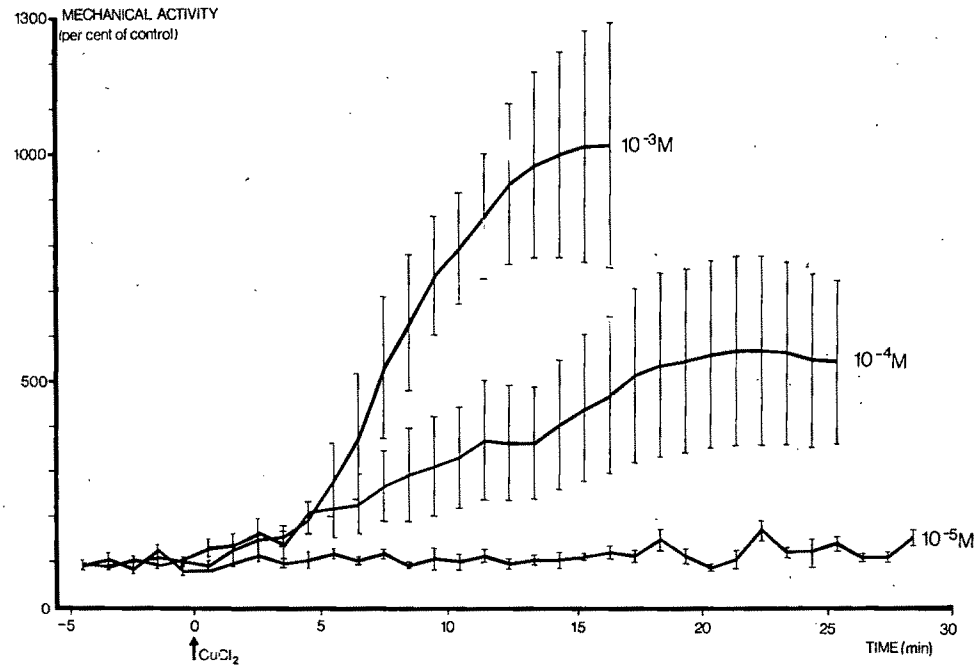


Fig. 8. Increase in mean active force of the rat portal vein in response to 10^{-5}, 10^{-4}, and 10^{-3}M $CuCl_2$, respectively, expressed as a percentage of the average control activity during five minutes prior to injection of the copper salt (arrow). Mean values ± S.E. (No. = 4) until maximal responses were obtained are illustrated.

which was, therefore, applied as a "standardized" initial stimulus in the experiments with copper. The spontaneous contractile frequency and amplitude were found to vary from patient to patient.

The clinical problem which prompted this study was to explore whether the copper liberated from a copper IUD might influence the activity of the smooth muscle of the human Fallopian tube. Therefore, it seemed relevant to study this activity in close connection to ovulation since the processes of both "picking up" the ovum and transport through the Fallopian tube have been intensely discussed in relation to IUD's. The majority of the patients were in the early secretory phase, although a small number was in the late follicular phase. It is possible that the variation in spontaneous activity between specimens taken from different patients could be ascribed to the variation in time in relation to ovulation.

Administration of copper in vitro was found to have a similar influence on the contractile activity of both the human oviduct preparation and the rat portal vein. In low concentrations (3×10^{-5}M), the most marked effect was a persistently increased contraction frequency. At higher concentrations (10^{-4}M to 10^{-3}M), a more dramatic increase in frequency was found which was associated with a reduction in contraction amplitude and a concomitant rise of the base-line level of tension. In response to high copper concentrations, the rhythmic contractions disappeared. This effect, which was irreversible, could not be explained on the basis of a lack of available substrates or oxygenation but probably reflects a toxic action of copper on the smooth muscle tissue. However, it is evident that prior to this irreversible effect the muscle was stimulated in a manner which caused considerable mechanical activity (Figs. 3 and 7).

The portal vein preparation was included in these experiments for two main reasons. First, it represents smooth muscle of the single-unit type from a different organ system of an experimental animal.[13] Thus, the finding of similar effects of copper on the human oviduct and on the rat portal vein may allow the conclusion that the influence of the metal described here relates to smooth muscle in general. Second, the rat portal vein is easily obtained, as compared to segments of the Fallopian tube, and the spontaneous activity of the vein is, furthermore, quite regular, which makes it particularly suitable for quantitative analysis of the influence of copper (Fig. 8).

The cellular mechanisms involved in the action of copper on smooth muscle have not been analyzed in detail. In smooth muscle of the single-unit type, however, the pattern of contractions normally reflects the electrical membrane activity. Therefore, the increased rate of contractions in response to copper in submaximal concentrations (see Figs. 2 and 7) suggests

that one effect is membrane excitation. This finding is in accordance with the previously observed convulsive action of Cu^{++} on brain tissue, which has been ascribed to an interference with the transport of ions across the nerve membrane.[17] Also, the contraction amplitude was found to be decreased by copper. This might be explained by its interaction with cellular respiration[6] or with the process of contraction.[12] Third, the tonic increase in force, which was observed in response to copper in high concentrations, could not be reduced by administration of smooth muscle relaxants such as papaverine and isoproterenol (unpublished observations). This third effect may be due to smooth muscle shrinkage as a result of protein denaturation.[23] The present results, in combination with previously reported effects of copper on other tissues, suggest possible mechanisms of action, but the clarification of these problems await future experiments on isolated smooth muscle.

In the present study, a comparison was made between the in vitro effect of $CuCl_2$ and metallic copper. No marked difference was found between these two forms of administration. This agrees with the findings of Brinster and Cross[2] who made similar comparisons in studies on the mouse blastocyst. It is evident that cupric ions, added to the bath solution as $CuCl_2$ or dissolved from metallic copper, exert profound effects on the motility of the human oviduct. The entire spectrum of copper effects in vitro was obtained at copper concentrations ranging from 10^{-5}M to 10^{-4}M. The copper dissolved from a Cu-IUD in situ may exist in various forms, both protein bound and as free divalent ions, the exact proportions of which are hard to evaluate. In the present experiments, performed in a protein-free model system, the concentration of free copper ions is known exactly.

Secretion was collected in the proximal part of the Fallopian tube in patients where a Cu-IUD with an area of 200 sq. mm. had been inserted for one to six weeks and analyzed for copper. A control group, without Cu-IUD's, was studied in parallel. In general, the copper concentration in the tubal secretions from patients with a Cu-IUD was twice that of the control group, with the highest value recorded after use of the IUD for only one week. The copper concentrations in the tubal secretion are not directly comparable to the in vitro situation since most of the copper in vivo is protein bound (see above). In a report by Oster,[15] cupric ions were shown to break disulfide bonds in serum albumin in a concentration-dependent way. This may change the affinity of copper to the protein. In addition, the albumin content of the secretion of the Fallopian tube varies throughout the menstrual cycle.[10] Such variations in the composition of this protein-rich fluid further increase the difficulties in calculating the concentrations of free copper. Thus, it would be of value if many patients scheduled for hysterectomy would use a copper IUD for variable times before operation and if these operations could be performed at different phases of the menstrual cycle.

In the present study, seven patients volunteered to wear Cu-IUD's for a short period prior to hysterectomy. In one of these cases, rhythmic activity was weak or absent. However, the possibility that this was due to technical difficulties cannot be excluded. In the other five cases, an apparently "normal" motility was registered, but, because the series is small, it is not possible to establish whether this activity qualitatively or quantitatively differs from the "normal" state. Further studies are in progress. The considerable problems involved in the crucial comparison between the in vivo and in vitro situations have been realized by other investigators. Brinster and Cross[2] studied the influence of $CuCl_2$ in buffer containing various amounts of albumin on the development of the mouse blastocyst. $CuCl_2$ in concentrations exceeding 2.5×10^{-5}M was lethal to the blastocyst when bovine serum albumin in a concentration of 1 mg. per milliliter was added to Krebs-Ringer bicarbonate buffer. When the albumin concentration was raised to 10 mg. per milliliter, the blastocyst could develop even if the $CuCl_2$ concentration was increased tenfold.

It is of clinical interest to determine if Cu-IUD's decrease the motility of the Fallopian tube, thereby causing an increased risk of ectopic pregnancies. A few cases of ovarian pregnancies in the presence of Cu-IUD's have recently been reported.[1, 19] Statistical data from the Cooperative Statistical Program of the Population Council do not show an increase in the number of tubal or ovarian pregnancies in women using plastic IUD's. This problem has also been discussed by Lehfeldt and colleagues[11] who claim that plastic IUD's "reduce uterine implantation by 99.5 per cent, tubal implantation by 95 per cent and the incidence of ovarian pregnancy not at all."

Differences in contraceptive mechanisms of plastic IUD's and Cu-IUD's are probable. The frequency of ectopic pregnancies in women wearing Cu-IUD's has not yet been evaluated in a large clinical series. However, the data so far available indicate that the over-all incidence of ectopic pregnancies is lower in women wearing Cu-IUD's as compared to women using no form of contraception.* From the present study it is not possible to draw clinical conclusions concerning the risk for ectopic pregnancies by use of a

*Johansson, E. D. B.: Personal communication.

Cu-IUD. Nevertheless, it is possible that the copper influence on the Fallopian tube motility provides a contraceptive action. Since the copper effect is biphasic, with an increase in motility in low concentrations followed by a decrease in higher concentrations, either an increased or decreased rate of ovum transport in vivo might occur. An excitatory influence on human Fallopian tube motility might be mediated by an effect of copper upon prostaglandin synthesis. Maddox[4] found that addition of copper to homogenates of seminal vesicles increases the synthetase activity of $PGF_{2\alpha}$, and Lau and colleagues[9] found an increase of $PGF_{2\alpha}$ in the endometrium of the mouse in the presence of intrauterine copper wire. Therefore, it seems possible that an important mechanism of contraceptive action by a Cu-IUD involves an increase of synthesis and release of $PGF_{2\alpha}$ which, in turn, would stimulate Fallopian tube motility.

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Reticulum-cell sarcoma of the cervix

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Four patients with primary reticulum-cell sarcoma of the cervix were described. One patient was treated with radical hysterectomy and lymphadenectomy. The pelvic lymph nodes contained metastatic cancer and the patient died shortly after with disseminating disease. The other three patients were treated with external radiation and vaginal and intrauterine radium application. The complete work-up failed to reveal cancer outside the pelvis or evidence of systemic disease. Two of these patients had an exploratory laparotomy with biopsies of pelvic and para-aortic lymph nodes and of the liver. One of these patients had a splenectomy, with no evidence of disease. Both patients are alive with no evidence of disease 3 and 10 years after their treatment. The third patient treated by radiation therapy died 2 years later with no evidence of disease. The importance of complete staging work-up and the advantage of radiation therapy in the treatment of reticulum-cell sarcoma of the cervix is emphasized.

MALIGNANT lymphomas (non–Hodgkin's lymphoma) usually present with generalized lymph-node involvement or massive organ infiltration with localized manifestations of lymphocytic or histiocytic lymphomas occurring in less than 20 per cent of the patients.[3] The most common primary site of extranodal malignant lymphoma or reticulum-cell sarcoma is the gastrointestinal tract, followed by the skin and bone.[3] In the rare case where the cervix is the primary site, the disease is unlikely to be localized.[1, 2, 4, 12] Thus the gynecologist very rarely is faced with the diagnosis and management of malignant lymphoma. This paper reports four cases of reticulum-cell sarcoma of the cervix (Figs. 1 and 2) with emphasis on treatment and follow-up.

Case reports

Four patients varying in age from 37 to 70, with primary reticulum-cell sarcoma of the cervix, were diagnosed and treated at the M. D. Anderson Hospital in Houston, Texas. Table I summarizes the diagnosis, treatment, and follow-up of each patient. For three patients (Nos. 1, 2, and 4) the main complaint was vaginal bleeding and examination revealed small but clinically diagnosable lesions in the cervix and vagina. In the fourth patient (No. 3), who had an abnormal Pap smear, a cone biopsy revealed reticulum-cell sarcoma.

All four patients had at least partial staging work-up following the procedures listed in Table II to determine stages described in Table III.[9] Patient No. 1, whose diagnosis was made by cervical biopsy, underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Lymph nodes were found to have metastatic cancer and the patient died 9 months later of disseminating disease. Patient No. 2, whose diagnosis was made by cervical biopsy, was treated with external radiation. She lived for 2 years free of disease and died of unrelated causes.

Patients Nos. 3 and 4 both underwent laparotomy in addition to the radiation treatment described in Table I. In patient No. 3, the laparotomy was prior to treatment and biopsies of the pelvic and para-aortic lymph nodes were negative. In patient No. 4 the laparotomy followed radiation and included splenectomy, hysterectomy, and bilateral salpingo-oophorectomy. Pelvic and para-aortic lymph node biopsies at this time were negative. Patients Nos. 3 and 4 are 10 and 3 year survivals, respectively.

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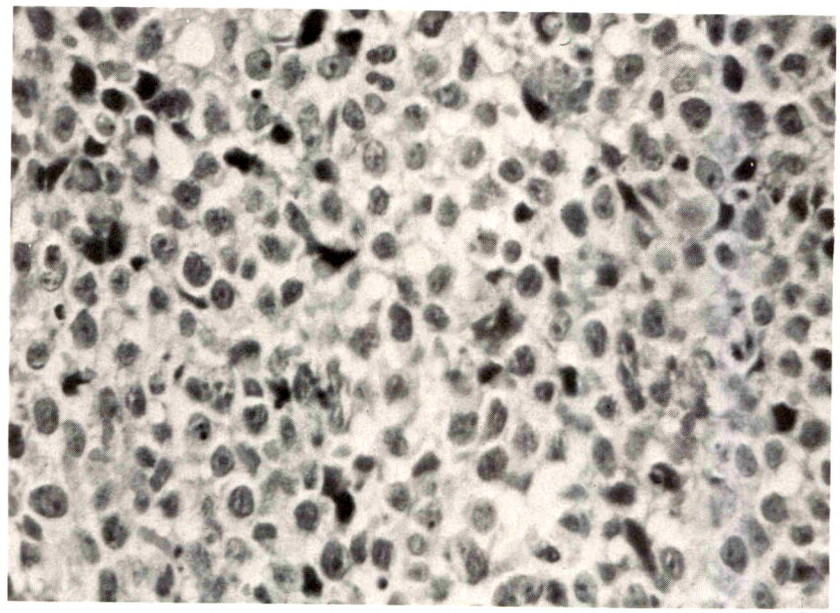


Fig. 1. Microscopic section showing reticulum-cell sarcoma of the cervix. Typical microscopic appearance of unicellular characteristic of reticulum-cell sarcoma.

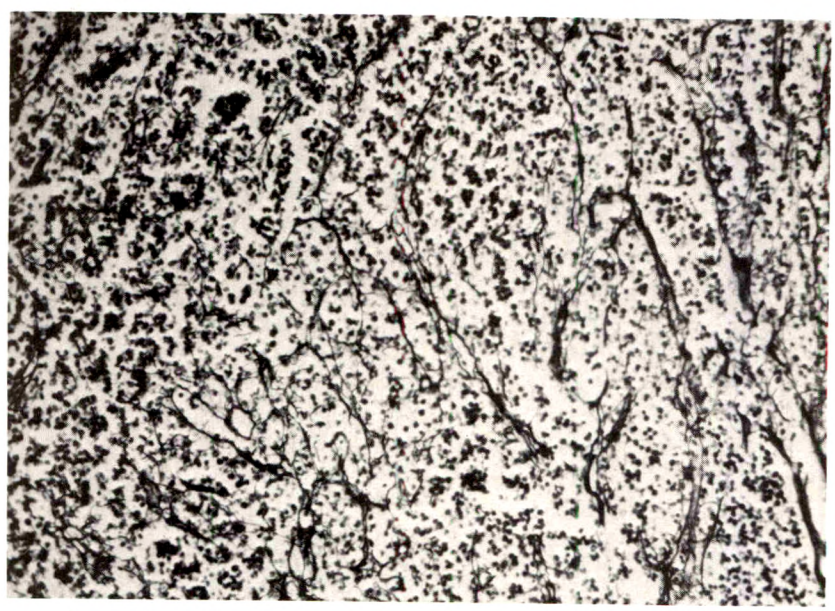


Fig. 2. Special Wilder stain showing reticulum fibers.

Comment

Patients with true localized disease are probably curable with radiation, especially if the lesion is localized to the cervix. Radium application plays an important role in the therapy of these patients due to the unique anatomic situation of the uterus. Extending radiotherapy to total nodal and total body irradiation may improve patients with more advanced disease.[7]

The treatment for reticulum-cell sarcomas confined to the cervix is difficult to outline from the few patients described in the literature or from the small number reported here. However, some general guidelines can be suggested regarding the management of these patients. A careful examination and work-up, as outlined in Table II, should be done before an assumption that a reticulum-cell sarcoma is confined to one histologic site. Staging laparotomies in patients with lymphoma is important since the medical work-up cannot necessarily distinguish early lymphomas in the spleen, liver, or lymph nodes.[5, 6, 8] Laparotomy should

Table I. Diagnosis, treatment, and follow-up of four patients with reticulum-cell sarcoma of the cervix

Pt. No.	*Age*	*Clinical stage*	*Staging laparotomy*	*Treatment*	*Final status*
1	43	Confined to cervix	Not done	Radical hysterectomy and pelvic lymphadenectomy	Dead—disseminating disease—9 mo.
2	70	Cervix and upper vagina	Not done	5,000 r in a 15 by 15 field in 5 weeks to the pelvis	No evidence of disease—2 yr. (dead without cancer)
3	43	Cervix and anterior vagina	Prior to treatment: pelvic and para-aortic lymph node biopsies—all negative	5,000 r in a 20 by 20 field in 5 weeks (pelvis and vaginal lesion); 4,000 r to para-aortic and inguinal lymph nodes; 1 intracavitary radium 4,380 mg. per hour	No evidence of disease—10 yr.
4	37	Cervix and vaginal vault	After treatment: splenectomy, liver biopsies, pelvic and para-aortic lymph node biopsies; hysterectomy and BSO; no residual disease	4,000 r in a 15 by 15 field in 4 weeks to pelvis; 1 radium application 6,000 mg. per hour	No evidence of disease—3 yr.

Table II. Procedures in staging work-up for reticulum-cell sarcoma

1. Careful clinical history
2. Thorough physical examination with careful description of all superficial lymph node areas
3. Roentgenographic examination of chest including tomograms if necessary
4. Liver function tests, particularly alkaline phosphatase and Bromsulphalein excretion
5. Biopsy of bone marrow, needle or open
6. Complete blood counts, urinalysis
7. Serum electrophoresis
8. Lower extremity lymphangiograms
9. Intravenous pyelography
10. Bone and liver scans in symptomatic patients
11. Staging laparotomy

Table III. Stages of extranodal presentation of reticulum-cell sarcoma

Stage I:
Disease in extranodal site alone or with involvement of one contiguous group or chain of lymph nodes
Stage II:
Disease in single extranodal site with involvement of two adjacent lymph node chains
Stage III:
A. Disease in single extranodal site and involvement of lymph nodes beyond limits of Stage II *without* extension to other side of diaphragm
B. Disease in two extranodal sites of different tissue origin
C. Disease in multiple extranodal sites in the same tissue of origin
B and C *without* lymph node involvement
Stage IV:
Extension of disease beyond the limits of Stage III

include exploration of the abdominal contents, splenectomy, and biopsy of the liver, the iliac para-aortic lymph nodes, and other areas. If the physical examination and laboratory work-up as outlined in Table II have been negative the patient who has reticulum-cell sarcoma of the cervix should have pretreatment laparotomy.

If the patient has reticulum-cell sarcoma confined to the cervix, the treatment should follow the general guidelines of treatment for squamous-cell cancer of the cervix, including intracavitary placement of radium as well as external radiation therapy. Total lymph node radiation, total body radiation, and combined chemotherapy should be deferred for the more advanced cases.[3, 10, 11] The excellent survival of three patients reported here treated with radiation appears to justify this treatment when the disease is confined to the cervix.

Summary

Four patients with primary reticulum-cell sarcoma of the cervix were described. One patient was treated with radical hysterectomy and lymphadenectomy. The pelvic lymph nodes contained metastatic cancer and the

patient died shortly after with disseminating disease.

The other three patients were treated with external radiation and vaginal and intrauterine radium application. The complete work-up failed to reveal cancer outside the pelvis or evidence of systemic disease. Two of these patients had an exploratory laparotomy with biopsies of pelvic and para-aortic lymph nodes and of the liver. One of these patients had a splenectomy, with no evidence of disease. Both patients are alive with no evidence of disease 3 and 10 years after their treatment. The third patient treated by radiation therapy died 2 years later with no evidence of disease.

The importance of complete staging work-up and the advantage of radiation therapy in the treatment of reticulum-cell sarcoma of the cervix are emphasized.

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Massive colonic bleeding and oral contraceptive "pills"

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Two patients on oral contraceptives who developed massive colonic bleeding have been presented. The clinical course and various studies suggest the mesenteric insufficiency syndrome as being a possible result of oral contraceptive effect on mesenteric vasculature. Although no definite histologic confirmation is available, the onset, course, and follow-up of these patients suggest contraceptive-induced massive colonic bleeding. The spectrum of oral contraceptive-induced colonic bleeding may vary from mucosal injury with massive colonic bleeding to transmural infarction. Only the clinical follow-up would determine the severity of the involvement and that would determine whether surgical intervention will be necessary.

ORAL CONTRACEPTIVES have been incriminated in the causation of pulmonary emboli, peripheral thromboemboli, and various visceral thromboembolic phenomenon. Although the occurrence of mesenteric infarction in young persons without a primary cause is rare, so far, in the literature, 12 documented cases of mesenteric ischemia and infarction as a result of oral contraceptive use have been reported. We have cared for two such patients in whom we feel the massive colonic bleeding resulted from the mesenteric mucosal injury due to oral contraceptives. A complete review of the available literature is presented. We emphasize the fact that awareness of this entity with early cessation of oral contraceptives may prevent the need for surgical intervention.

Case report

Case 1. A 48-year-old white woman presented to the emergency center with a 12 hour history of bloody diarrhea. On the day of admission, the patient had frequent bowel movements progressing to watery diarrhea, and then to frankly bloody diarrhea by the time of admission. The diarrhea was accompanied by cramping lower abdominal pain but no fever, chills, nausea, or vomiting.

The past history was negative for symptoms of ulcer, malabsorption syndrome, or any type of colitis. The patient had always been in good health and was not taking any chronic medications except for birth control pills (Ortho-Novum 1/80) for the past 5 years. She reportedly had no side effects from the contraceptives.

Physical examination at the time of admission revealed a moderately obese white woman in no acute distress. The vital signs were stable, with a blood pressure of 132/84 mm. Hg and a pulse of 86. She was comfortable except when episodes of cramps would occur. The only positive finding were mild tenderness to deep palpation in the lower quadrants and bright red stool on rectal examination. On admission, the hemoglobin was 13.9 and an acute abdominal series was negative. An emergency barium enema was performed and revealed spasm, edema, and thumb-printing of the cecum and ascending colon (Fig. 1). There was no associated colonic disease present. Sigmoidoscopy failed to reveal any evidence of colitis or the source of the bleeding.

Because of the patient's lack of clinical symptoms, she was treated nonoperatively with intravenous fluids, serial hemoglobins, and withdrawal of the birth control pills. Over the next 6 hours, the pain and diarrhea subsided. She was started on Prednisone, 10 mg. four times a day, as a therapy for vasculitis due to estrogen, and had further resolution of her symptoms. Twenty-fours after admission, the patient had no further bleeding and was asymptomatic.

On the seventh hospital day, she had a repeat barium enema which was essentially normal. She was taken off

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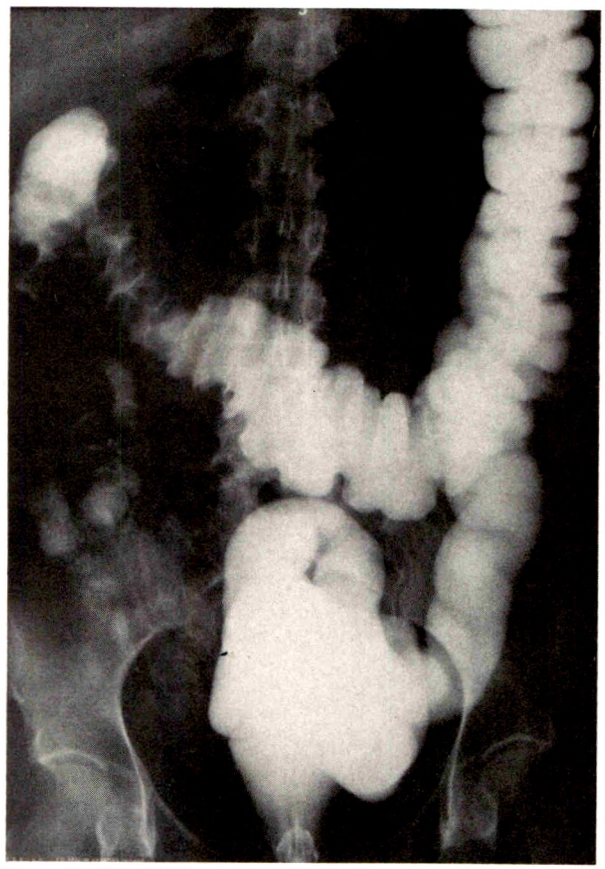


Fig. 1. Barium enema revealed spasm, edema, and thumb-printing of the cecum and ascending colon.



Fig. 2. Barium enema showed thumb-printing and spasm in the ascending and transverse colons.

the birth control pills permanently and tapered off the steroids over the ensuing 2 weeks. She has remained asymptomatic since that time.

Case 2. A 19-year-old white woman who was admitted with a 2 week history of cramping lower abdominal pain and a 5 day history of passing bright red stool per rectum. Bleeding became more prominent and the patient was admitted to the hospital. Sigmoidoscopy revealed internal hemorrhoids with no mucosal lesions.

Past history was significant only in that the patient had been taking ASA, eight to 10 per week for the past several weeks. She had been on birth control pills (Orval) for approximately 3 months.

On admission the hemoglobin was 13.3 but dropped to 9.7 over the next 48 hours. Coagulation studies were normal except for fibrinogen, which was slightly elevated at 526 mg. (normal, 200 to 400).

A Levin tube was placed overnight, but did not drain any blood. The barium enema revealed thumb-printing and spasm in the ascending and transverse colon (Figs. 2 and 3). The UGI series were negative.

The birth control pills were withdrawn, with spontaneous cessation of her bleeding, and she became asymptomatic.

Comment

Mesenteric thrombosis of the bowel is rare; when it does occur, it is usually found in the elderly, the arteriosclerotic, the diabetic, and more frequently in the male patient. Oral contraceptives have been shown to cause increased incidence of thrombotic episodes.[1] The thrombogenic potential of oral contraceptives appears to reside in the estrogenic component.[2] Additional data are needed on the nature, frequency, and significance of the vascular lesions seen in oral contraceptive users and on the effect of oral contraceptives on platelet function.

Vessey and Doll[3] concluded, after extensive review, that recent evidence "strengthens the belief that oral contraceptives are a cause of venous thromboembolism.

Another restropective study done by Sartwell and co-workers[4] in the United States confirmed these

findings. The mesenteric ischemia resulting from oral contraceptive use may range in severity from mild hematochezia to gangrene of the bowel.

The triad of symptoms observed by others (lower abdominal pain, bloody bowel movements, and a characteristic radiologic finding of edema and thumb-printing in the bowel wall) were also observed by us. In our patients, the ascending colon and hepatic flexure were mainly involved.

Most of the cases reported in the literature underwent exploratory surgery before a final diagnosis of mesenteric thrombosis was made. Since the spectrum may range from mucosal infarction to gangrene of the bowel, from vasculitis to mesenteric venous thrombosis and gangrene, we recommend that treatment should also range from careful observation with cessation of oral contraceptives to exploratory laparotomy and resective surgery in extreme cases. A careful history to rule out other etiologic factors is essential. However, when one is faced with massive colonic bleeding in a woman of child-bearing age who has been on oral contraceptives, she must certainly be considered to have this entity. Also if the patient is in minimal distress, with some mild abdominal pain and with apprehension associated with passage of fresh blood or clots, but no clinical sign of acute abdomen, we recommend careful observation. Immediate sigmoidoscopy to rule out ulcerative colitis and an emergency barium enema may confirm the clinical impression. A mesenteric angiogram may be of some help, but often this does not reveal any abnormalities, since the occlusion occurs in the peripheral branches.

Increased thrombin generation, decrease in antithrombin III activity,[5] increase in platelet adhesive, and increase in the effect of various clotting factors have been reported in literature pertaining to estrogen use.[6, 7] Degenerative and proliferative changes in the endothelium and deeper layers of small arteries and veins have also been demonstrated with estrogen use.[8] How far can one correlate these findings with clinical thrombosis is still controversial. Without going into this controversial discussion, we merely state that many reports of visceral vascular occlusive disease have been published in patients who are least likely to have these complications, due to the absence of other predisposing factors. In these cases, the relationship of the drug to the illness seems causally related.

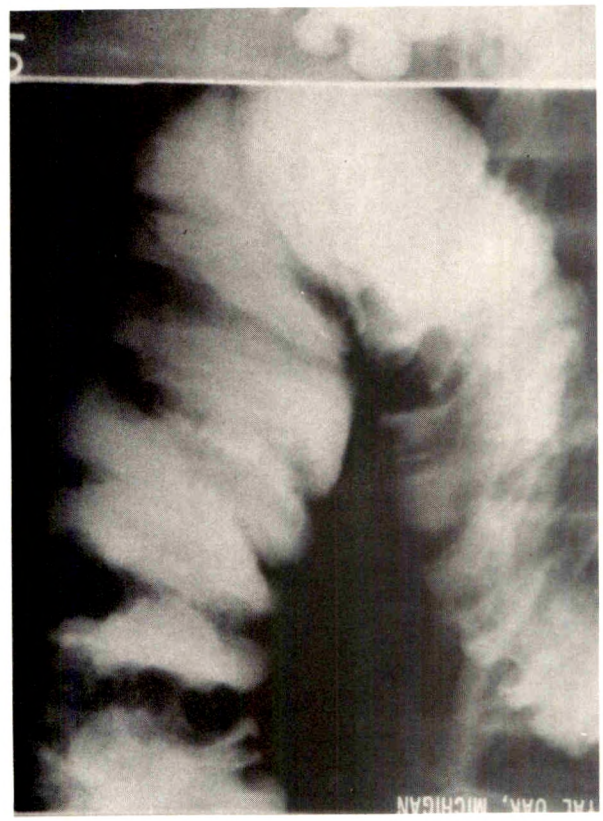


Fig. 3. Barium enema showed thumb-printing and spasm in the ascending colon.

We do not concur with Brennan and associates[9] regarding cessation of oral contraceptives in women who develop vague abdominal pain. These women should be investigated thoroughly with sigmoidoscopy, barium enema, and other hematologic studies such as changes in thrombin generation, antithrombin III activity, various coagulation parameters, platelet adhesive study, and the newly described thromboelastographic study[10] to screen for high-risk groups.

If these parameters suggest "high risk" of thrombogenesis in these patients, the contraceptive pills may be discontinued and alternative nonhormonal modes of contraception instituted.

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Effect of clomiphene citrate upon amount and duration of human menopausal gonadotropin therapy

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Human menopausal gonadotropin (HMG) was given to 10 patients who failed to ovulate after treatment with clomiphene citrate. Prior to one or more treatment courses, 200 mg. of clomiphene were administered daily for 5 days; at least one other treatment course was not preceded by clomiphene. Before therapy, progesterone in oil was administered and serum FSH, LH, and estrogen were measured. Those patients who had normal serum FSH levels and had withdrawal bleeding following progesterone had a reduction in amount and duration of HMG therapy when pretreated with clomiphene. There was no alteration in HMG requirements for those patients with low serum FSH who did not withdraw. Thus, sequential clomiphene-HMG therapy is of benefit only for those women with normal serum FSH levels and is the treatment of choice.

CLOMIPHENE CITRATE (Clomid) and human menopausal gonadotropins (HMG, Pergonal) are the drugs used most commonly to treat infertility secondary to anovulation. Gonadotropin therapy is expensive and inconvenient and is associated with a greater incidence of complications, such as ovarian hyperstimulation and multiple gestations, than is clomiphene citrate.[1]

However, a method of decreasing the duration of gonadotropin therapy and/or reducing the dose of HMG required to induce ovulation would facilitate therapy. In 1967, Cox and associates[2] reported the induction of ovulation in two patients following combined clomiphene-HMG administration. Neither patient had ovulated when these two drugs had been administered separately. These investigators suggested that one effect of clomiphene citrate may be sensitization of the ovaries to gonadotropin stimulation. Two years later, Crooke and associates[3] performed ovarian sensitivity tests on anovulatory women. They demonstrated that clomiphene citrate augmented the activity of pituitary follicle-stimulating hormone (FSH) in six of 15 patients by a factor of 173 per cent. The success of sequential and simultaneous administration of both drugs has been confirmed by many investigators.[4, 5] However, it has also been reported that not all patients who receive treatment with clomiphene citrate in addition to HMG have a reduction in the amount of HMG necessary to achieve ovulation.[6]

This study was undertaken in order to determine if it was possible prior to therapy to identify which patients would benefit by treatment with clomiphene citrate prior to HMG.

In our clinic, clomiphene citrate is administered by an individualized, graduated treatment regimen.[7] With this method of therapy, ovulation was induced in 91.4 per cent of 105 anovulatory patients and, of the 42 patients with no other demonstrable infertility factors, 85.7 per cent conceived. Treatment with gonadotropins is limited to those patients who fail to ovulate following the administration of clomiphene citrate, 250 mg. daily for 5 days, followed by 10,000 I.U. of human

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Table I. Patients receiving HMG/HCG and sequential clomiphene citrate/HMG/HCG

	Patient				
	M. L.	*C. S.*	*S. K.*	*J. B.*	*B. G.*
Diagnosis	Hypothalamic-pituitary failure	Sheehan's syndrome	Empty sella syndrome	Hypothalamic failure	Isolated gonadotropin deficiency
Age	26	34	33	30	27
Parity	0000	2001	0000	0000	0000
Menstrual history	Primary amenorrhea	Postpartum amenorrhea	Primary amenorrhea	Post-pill amenorrhea	Post-pill amenorrhea
Ovarian biopsy	Marked capsular sclerosis, reduced number of follicles	Reduced number of follicles		Normal	

	Patient				
	H. L.	*O. B.*	*K. S.*	*P. McL.*	*C. G.*
Diagnosis	Hypothalamic-pituitary dysfunction	Hypothalamic-pituitary dysfunction	PCO	PCO	PCO
Age	27	27	29	27	23
Parity	0020	0000	0000	0000	0000
Menstrual history	Oligomenorrhea	Oligomenorrhea	Secondary amenorrhea	Post-pill amenorrhea	Primary amenorrhea
Ovarian biopsy	Reduced number of follicles	Normal	PCO	PCO	

chorionic gonadotropin (HCG). Failure to ovulate, not failure to conceive, is the only indication used in our clinic for HMG therapy.

Materials and methods

Patients. Ten patients between 23 and 34 years of age with anovulatory infertility of 3 to 10 years' duration were treated with HMG (Table I). Three patients had primary amenorrhea, five had secondary amenorrhea, and two had oligomenorrhea. None had galactorrhea. Each had failed to ovulate following the administration of clomiphene citrate, 250 mg. daily for five days, followed by 10,000 I.U. of HCG.

Pretreatment studies. All patients were administered 100 mg. of progesterone in oil intramuscularly. Five of the 10 patients did not have withdrawal bleeding after this dose nor after subsequent treatment with 200 mg. of progesterone in oil. FSH, luteinizing hormone (LH), and immunoreactive estrogens were measured in duplicate serum samples by previously described radioimmunoassay (RIA) techniques.[8, 9] The 95 per cent confidence limits of hormonal values as determined by linear transform method during the follicular phase of normal ovulatory cycles for FSH are 3.2 to 9.0 mI.U. per milliliter; for LH, 5.0 to 25.0 mI.U. per milliliter; and for estrogens, 20 to 270 pg. per milliliter. According to the criteria of Kletzky and associates,[10] the results of these assays were interpreted in conjunction with the response to intramuscular progesterone to establish a diagnosis. All five patients who had no withdrawal bleeding had hypothalamic-pituitary failure. Of those who did have withdrawal bleeding, three had polycystic ovarian disease (PCO) and two had hypothalamic-pituitary dysfunction.

Growth hormone stimulation and cortisol stimulation tests with insulin-induced hypoglycemia were normal in four of the five patients who did not have withdrawal bleeding. The patient with Sheehan's syndrome (C. S.) had a normal cortisol response following insulin; however, there was no growth hormone response. Visual field examinations were normal in these five patients. X-rays of the sella turcica were normal in all patients in this group except S. K., who had enlargement without erosion. The diagnosis of the empty sella syndrome was established by pneumoencephalography. Infusions of thyroid-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) established the diagnosis of an isolated gonadotropin deficiency in B. G. and of hypothalamic failure in J. B.

Laparoscopy or culdoscopy was performed in eight patients. All had bilateral tubal patency demonstrated by chromopertubation. The remaining two patients, B. G. and K. S., had tubal patency demonstrated by

uterotubal insufflation of CO_2. Ovarian biopsy was performed in seven patients (Table I). All gonads had follicles present.

Other studies including CBC, serum electrolytes, liver, renal, and thyroid function tests, VDRL, urinalysis, cervical cytology, and culture for *N. gonorrhoeae* were normal in all patients. The husbands of each of the patients had a normal semen analysis.

Treatment. In one or more treatment cycle, each of the patients was administered clomiphene citrate, 200 mg. per day, for the 5 days immediately preceeding the administration of HMG. Additionally, in one or more treatment cycle each patient was treated with HMG without prior therapy with clomiphene citrate. The selection of which method of treatment was used initially was not randomized.

In each treatment cycle HMG was administered daily in individualized doses whether or not clomiphene citrate had been given previously. HMG was given in sequentially increasing amounts every 3 to 4 days until the desired estrogen production was achieved. Estrogen production was estimated by daily measurements of serum immunoreactive estrogens.[9]

In all treatment cycles, when serum estrogen concentrations exceeded 500 pg. per milliliter and the cervical mucus was of good quality, a fractional postcoital test was performed and HMG was discontinued. Then 10,000 I.U. of HCG were administered 24 to 36 hours after the last dose of HMG. The patients were again instructed to have intercourse. Two subjects, B. G. and J. B., never developed cervical mucus of good quality despite excellent estrogen production. Postcoital tests were always poor and therefore 24 hours after HCG administration inseminations of their husbands' semen were performed by means of a cervical cup.

In those patients who had evidence of ovulation following treatment with HMG, but who had a short luteal phase, subsequent treatment cycles included augmentation with 3,000 I.U. of HCG 4 and 8 days after the initial injection of HCG.

Seven days after HCG administration, the serum progesterone level was measured by RIA as previously described.[11]

The 10 patients were treated with HMG/HCG for a total of 49 cycles, 32 without clomiphene pretreatment and the remaining 17 cycles preceeded by clomiphene citrate therapy.

Results

Pretreatment hormone measurements. The 10 patients were divided into two groups of five each, based upon whether or not they had withdrawal bleeding after receiving progesterone. The five patients who did not withdraw after intramuscular progesterone had low serum FSH levels between 1.5 and 3.5 mI.U. per milliliter, whereas FSH levels in those who had withdrawal bleeding were between 5.3 and 6.8 mI.U. per milliliter (Table II). These differences are statistically significant ($p < 0.01$). Serum LH levels ranged between 2.2 and 12 mI.U. per milliliter in those patients who did not withdraw and between 9.8 and 60 mI.U. per milliliter in those patients who did, whereas immunoreactive estrogen levels were between 22 and 60 pg. per milliliter in the group that did not bleed and between 68 and 159 pg. per milliliter in those who did bleed.

Table II. Response to intramuscular progesterone in oil and serum FSH, LH, and immunoreactive estrogens in study group prior to treatment

	Patient				
	M. L.	*C. S.*	*S. K.*	*J. B.*	*B. G.*
Progesterone withdrawal	—*	—	—	—	—
FSH† (mI.U./ml.)	2.1	3.0	1.5	3.5	1.9
LH† (mI.U./ml.)	2.3	4.8	12	3.0	2.2
Estrogen† (pg./ml.)	32	22	40	60	34
	Patient				
	H. L.	*O. B.*	*K. S.*	*P. McL.*	*C. G.*
Progesterone withdrawal	+‡	+	+	+	+
FSH† (mI.U./ml.)	6.5	6.8	6.8	5.3	6.4
LH† (mI.U./ml.)	14	9.8	34	60	33.4
Estrogen† (pg./ml.)	128	159	68	106	90

*No withdrawal bleeding.

†Normal follicular phase levels: FSH = 3.2 to 9.0 mI.U./ml.; LH = 5.0 to 25.0 mI.U./ml.; estrogen = 20 to 270 pg./ml.

‡Withdrawal bleeding.

Ovulation and pregnancy. Forty-seven of the 49 (96 per cent) cycles were presumed to be ovulatory based upon a serum progesterone level of 3 ng. per milliliter or greater,[12] associated with a basal body temperature rise of 13 or more days followed by spontaneous menses or pregnancy. Six of the 10 (60 per cent) patients became pregnant and eight of the 47 (17 per cent) ovulatory cycles resulted in pregnancy. Of these eight pregnancies, four terminated in spontaneous abortion between 5 and 10 weeks of gestation, three patients were delivered at term of a single infant, and

Table III. Effect of pretreatment with clomiphene citrate upon the mean number of ampules and mean number of treatment days in patients with low serum FSH and no withdrawal bleeding after intramuscular progesterone

		HMG/MCG		*CC/HMG/HCG*	
Pt.	*FSH*	*Mean ampules*	*Mean days*	*Mean ampules*	*Mean days*
M. L.	2.1	72	9.7	70	8
C. S.	3.0	49	7.5	86	14
S. K.	1.5	30	9	28	8
J. B.	3.5	19	7	19	7
B. G.	1.9	36	7	62	12
$\bar{X}$		52	8.9	53	9.8

Table IV. Effect of pretreatment with clomiphene citrate upon the mean number of ampules and the mean number of treatment days in patients with normal serum FSH and withdrawal bleeding after intramuscular progesterone

		HMG/HCG		*CC/HMG/HCG*	
	FSH	*Mean ampules*	*Mean days*	*Mean ampules*	*Mean days*
H. L.	6.5	10	5	4	2
O. B.	6.8	22	9	7	3.7
K. S.	6.8	34	10	18	6
P. McL.	5.3	12	6	7	3.5
C. G.	6.4	18	8	11	4
$\bar{X}$		20	7.5	8	3.5

one patient delivered viable triplets at 37 weeks. Mild ovarian enlargement which resolved spontaneously occurred in three cycles (six per cent). Thirty-one of the 32 HMG/HCG without clomiphene cycles were ovulatory, resulting in six of the eight pregnancies, whereas 16 of the 17 clomiphene-HMG/HCG cycles were ovulatory and two pregnancies occurred. The three ovarian cases of ovarian enlargement were minimal and occurred in the HMG/HCG cycles.

Effect of pretreatment with clomiphene citrate. With respect to both duration of treatment and the amount of HMG required to achieve adequate follicular maturation, a significant difference was noted between the two groups of patients (Tables III and IV). The mean number of ampules of HMG per treatment cycle required to achieve adequate follicular maturation by the group with low serum FSH (52) was higher than those with the normal FSH values (20) ($p < 0.001$).

Those patients who had withdrawal bleeding after intramuscular progesterone administration and normal FSH levels had a marked reduction in both the mean number of ampules of HMG required to induce ovulation, from 20 to eight ($p < 0.001$), and in the duration of therapy, from 7.5 to 3.5 days ($p < 0.001$), when HMG treatment was preceded by clomiphene. The group of patients with no withdrawal bleeding and low FSH levels had no reduction in the amount of HMG, 52 and 53 ampules ($p > 0.05$), nor the number of days it was administered, 8.9 and 9.8 days ($p > 0.05$).

Serum immunoreactive estrogens were measured before and after clomiphene administration. Estrogen levels markedly increased after clomiphene was administered in those patients with a normal FSH (Fig. 1). No increase in estrogen levels occurred following clomiphene therapy in the group of patients whose FSH levels were low (Fig. 2).

Comment

The results of this study confirm that only certain patients who require HMG therapy to induce ovulation will need less drug if they are treated with clomiphene citrate immediately prior to HMG. It has not been previously shown if there were any criteria for determining in which patients pretreatment with clomiphene citrate would be beneficial, but the results of this study indicate that it is possible to utilize certain criteria to differentiate those patients. The characteristics of those anovulatory patients who will require less HMG after pretreatment with clomiphene citrate are (1) withdrawal bleeding following intramuscular progesterone and (2) a normal serum FSH.

Clomiphene has been shown to compete with estradiol for binding sites in the hypothalamus and pituitary gland.[13, 14] During and immediately after the administration of clomiphene citrate to patients with a functional hypothalamic pituitary axis, plasma FSH and LH levels rise.[15] These increased gonadotropins stimulate ovarian production of estradiol. Additionally, clomiphene has been shown to exert a direct effect upon the ovary by increasing conversion of androstenedione to estradiol and estriol.[16] Following treatment with clomiphene citrate there is a gradual rise in serum estrogen levels as the result of one or both of these mechanisms. This rise in estrogen production is indicative of partial ovarian follicular maturation. Those amenorrheic patients who have withdrawal bleeding after intramuscular progesterone and who have a normal serum FSH will achieve partial ovarian follicular maturation during pretreatment with clomiphene citrate, as shown by an increase in their

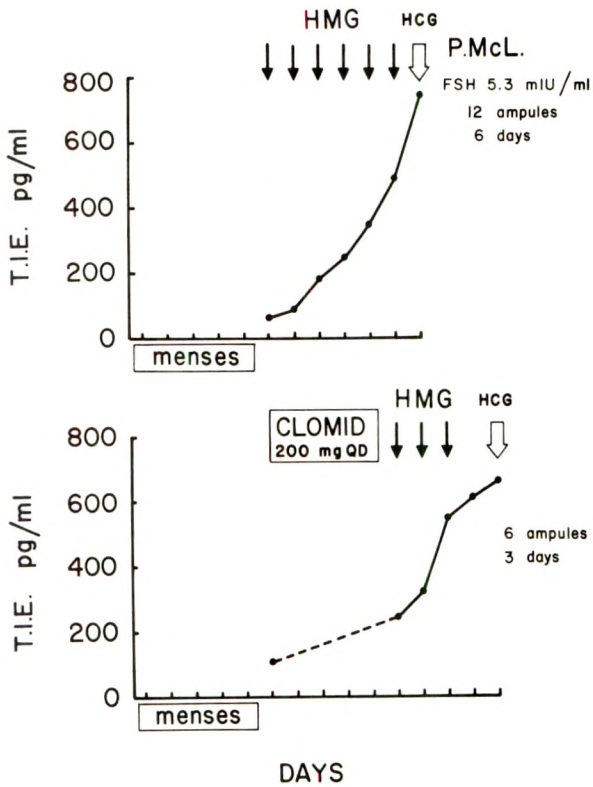


Fig. 1. Effect of clomiphene pretreatment upon total immunoreactive estrogens (TIE) and HMG requirements in a patient with a normal serum FSH who does bleed after intramuscular progesterone.

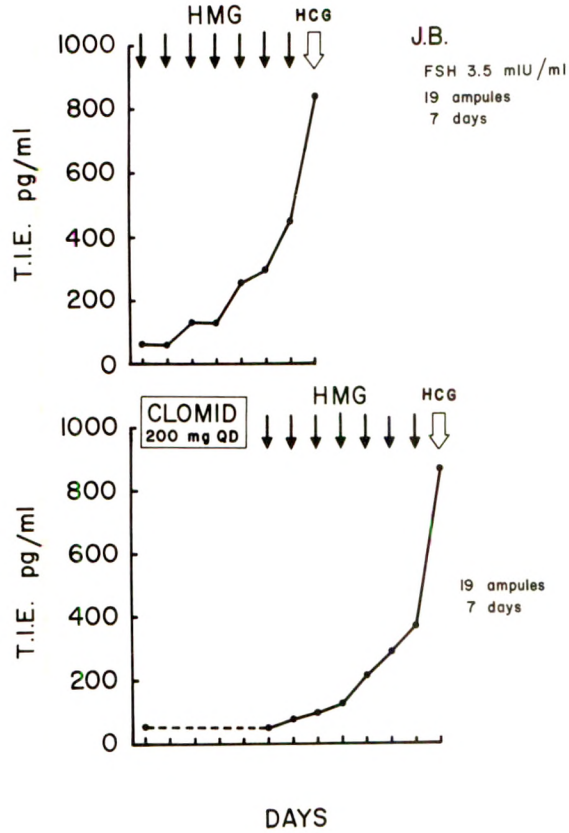


Fig. 2. Effect of clomiphene pretreatment upon total immunoreactive estrogens (TIE) and HMG requirements in a patient with a low serum FSH who does not bleed after intramuscular progesterone.

serum estradiol levels. The partially mature follicle will require less stimulation with HMG to reach the proper preovulatory condition. For instance, H. L. required only four ampules of HMG to reach a serum estradiol level of 500 to 1,000 pg. per milliliter in those cycles which included clomiphene citrate pretreatment and 10 ampules when clomiphene citrate was not administered. The dose of four ampules is less than that advised by those who administer a fixed amount of clomiphene-HMG and do not measure estrogen production. Hence, daily monitoring of serum estrogens must continue to be performed in all patients who receive HMG with or without clomiphene citrate to reduce the likelihood of hyperstimulation.

When a negative response to progesterone is obtained, certain additional tests should be performed prior to administering HMG. An elevated serum FSH level will identify those patients with ovarian failure who should not be treated. Second, those with low or normal serum FSH levels should be further evaluated to rule out a pituitary tumor. Minimal investigation includes an x-ray of the sella turcica and visual field examination. It is not necessary to perform these studies in those patients who bleed after progesterone provided they do not have galactorrhea.[10]

Selection of patients for combined clomiphene-HMG therapy may be made on the basis of the administration of intramuscular progesterone and a single determination of serum FSH. Because the incidence of ovulation with this combination regimen is similar to that following HMG alone, while being less costly and of shorter duration, it is the treatment of choice for those patients with a normal FSH who bleed following progesterone but who do not ovulate despite treatment with high doses of clomiphene citrate. Conversely, those patients who have low serum FSH levels and do not withdraw to intramuscular progesterone will not experience a reduction in HMG requirement after clomiphene pretreatment and should not be treated with clomiphene before HMG.

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Ortho-Novum 1/80□21 and Ortho-Novum 1/80□28

Description: Each white ORTHO-NOVUM 1/80 tablet contains 1 mg of the progestational substance, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol. Each green tablet in the 28-day regimen contains inert ingredients.

Actions: ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of contraceptives.

Precautions: 1. A thorough history and physical examination should be performed bef prescribing oral contraceptives and periodically during their administration and shc include special reference to breasts and pelvic organs, including Papanicolaou smear si estrogens have been known to produce tumors, some of them malignant, in five specie subprimate animals. 2. Endocrine and possibly liver function tests may be affected by tr ment with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28. Therefore, if such te are abnormal in a patient taking ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□2 is recommended that they be repeated after the drug has been withdrawn for two month Under the influence of estrogen-progestogen preparations, pre-existing uterine fibror mata may increase in size. 4. Because these agents may cause some degree of fluid re tion, conditions which might be influenced by this factor, such as epilepsy, migra asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bl ing, and in all cases of irregular bleeding per vaginam, nonfunctional causes should borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures indicated. 6. Patients with a history of psychic depression should be carefully observed the drug discontinued if the depression recurs to a serious degree. 7. Any possible influe of prolonged ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy on pituit ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in gluc tolerance has been observed in a significant percentage of patients on oral contracepti The mechanism of this decrease is obscure. For this reason, diabetic patients should carefully observed while receiving ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□ therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatm with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 may mask the onset of climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/80□21 ORTHO-NOVUM 1/80□28 therapy when relevant specimens are submitted. 11. Susc ble women may experience an increase in blood pressure following administration of traceptive steroids. 12. Cholestatic jaundice has been reported in users of contraceptives. If this occurs ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□ should be discontinued. This condition is more likely to occur in patients who h experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic ja dice of pregnancy should be carefully observed during ORTHO-NOVUM 1/80□21 ORTHO-NOVUM 1/80□28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistic significant association has been demonstrated between use of oral contraceptives and following serious adverse reactions: thrombophlebitis, pulmonary embolism, ceret thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has b neither confirmed nor refuted for the following serious adverse reactions: neuro-oc lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without ir abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contra tives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bl ing), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during after treatment, edema, chloasma or melasma, which may persist, cholestatic jaund migraine, rash (allergic), mental depression, change in weight (increase or decrea breast changes (tenderness, enlargement and secretion), changes in cervical erosion cervical secretions, suppression of lactation when given immediately post-partum, ris blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contra tives, an association has been neither confirmed nor refuted: anovulation post-treatm which tends to occur more frequently in women with a history of menstrual disord premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndro headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hir ism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptic itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hep function—increased sulfobromophthalein retention and other tests; coagulation tes increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increas platelet aggregability; thyroid function—increase in PBI, and butanol extractable prot bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determ tion.

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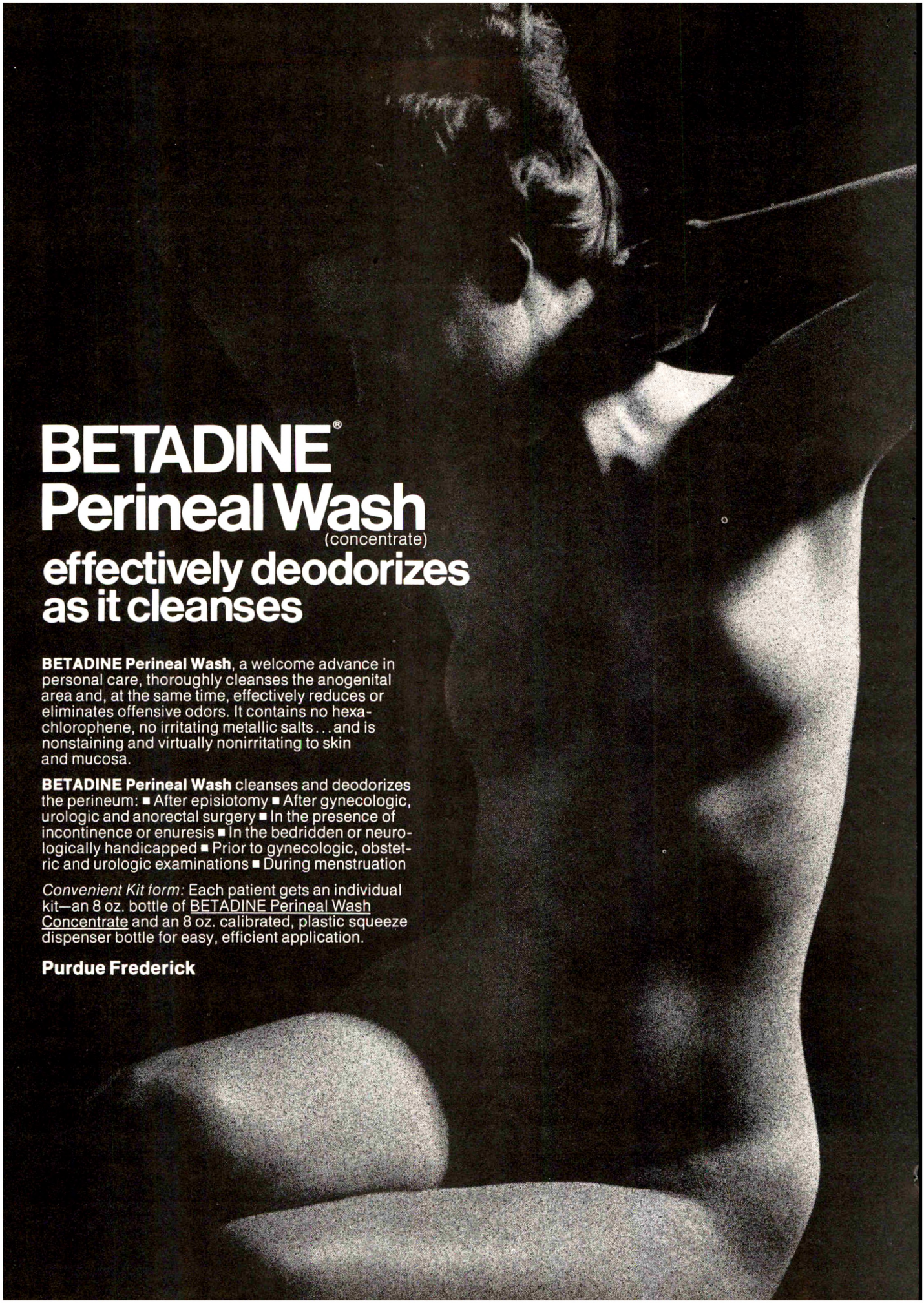
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CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and 6 references. Illustrations or additional references require a proportionate reduction in total words.

Limitation of the specific serum radioimmunoassay for human chorionic gonadotropin in the management of trophoblastic neoplasms

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Two cases of recurrent trophoblastic disease are presented in which human chorionic gonadotropin was detected in assays of urine concentrates at a time when serum levels were undetectable by a sensitive and specific β-subunit radioimmunoassay. The potential greater usefulness of measurements of urinary concentrates is discussed.

DEPENDABLE, sensitive assays for human chorionic gonadotropin (HCG) are essential for the diagnosis and treatment of women with gestational trophoblastic neoplasms. For these purposes, bioassays of total urinary gonadotropins have been used successfully despite the fact that such assays distinguish pituitary gonadotropins from HCG exclusively on the basis of the quantities of total gonadotropic activity found in the concentrates of 24 hour urine specimens.[1] Radioimmunoassays (RIA's) specific for HCG in serum have also been used successfully,[2, 3] but practical constraints on obtaining and concentrating large quantities of serum impose limitations on the effective sensitivity of such assays. Since the concentrations of HCG in urine and serum are approximately equivalent, assays of urine concentrates are potentially more effective than serum assays for detecting the persistence of minute amounts of hormone-secreting trophoblastic tissue. To demonstrate the potential usefulness of the measurement of HCG in urine concentrates and the difficulties of relying solely on serum RIA determinations, we wish to report two cases of recurrent trophoblastic disease following chemotherapy in which HCG was detected in assays of urine concentrates at a time when serum levels were undetectable by a sensitive and specific RIA.

From the Reproduction Research Branch, National Institute of Child Health and Human Development, National Institutes of Health.

Reprint requests: Dr. Griff T. Ross, Bldg. 10, Room 12N-202, NICHD, NIH, Bethesda, Maryland 20014.

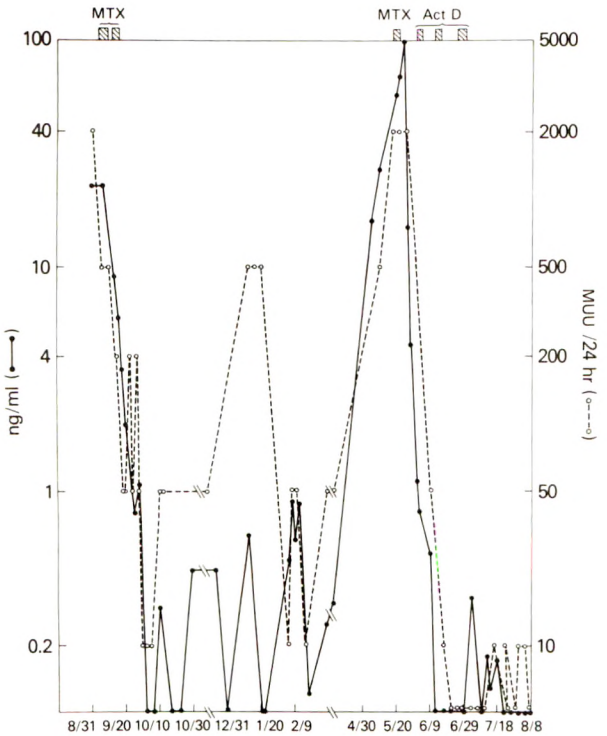


Fig. 1. Serum HCG levels (—●—●—●—) and urinary bioassay levels (—○—○—○—) in Patient M. Y. Y. Serum HCG was measured by RIA with an antibody specific for the HCG–β-subunit.[2] Urinary HCG was measured with the mouse uterine weight bioassay.[1] Normal values are 1 ng. per milliliter or less in the serum assay[2] and less than 200 M.U.U. in the urine assay.[1] Each course of methotrexate was 20 mg. intramuscularly every day for five days, and each course of actinomycin D was 0.5 mg. intravenously every day for five days.

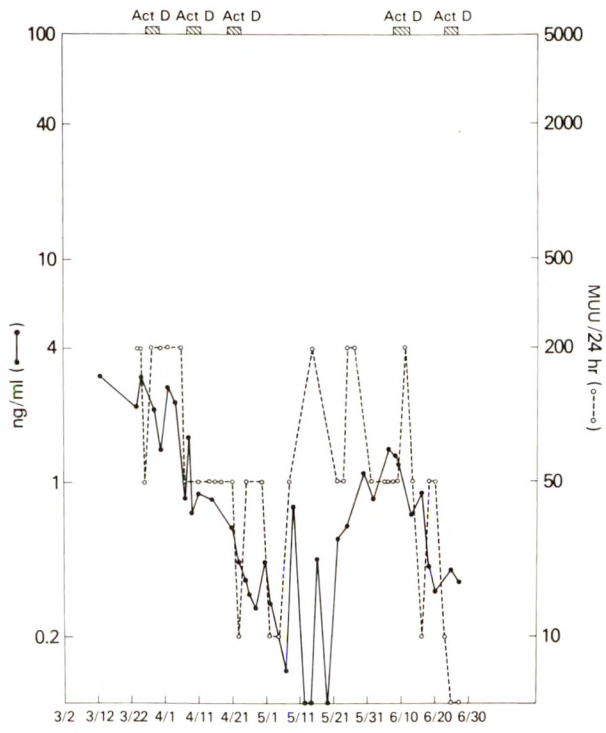


Fig. 2. Serum HCG levels (—●—●—●—) and urinary bioassay levels (—○—○—○—) in Patient S. G. Normal values are the same as in Fig. 1. Each course of actinomycin D was 0.5 mg. intravenously every day for five days.

Case reports

M. Y. Y., a 34-year-old Chinese woman, gravida 1, para 0, molar pregnancy 1, had dilatation and curettage in October, 1973, for persistent vaginal bleeding. The pathologic diagnosis was benign hydatidiform mole. She received no further therapy until August, 1974, when a routine chest x-ray revealed a left–upper-lobe "coin" lesion. Serum HCG by RIA[2] was 23 ng. per milliliter, and the bioassay of kaolin-acetone concentrates of 24 hour urine specimens[1] was positive at 2,000 mouse uterine units (M. U. U.). She was given combination oral contraceptive pills* to suppress pituitary gonadotropin secretion and begun on methotrexate as chemotherapy for the gestational trophoblastic neoplasm. The clinical course of the patient is summarized in Fig. 1. Levels of HCG rapidly declined, and after two courses of methotrexate the hormone was no longer detected in the serum. Therapy was stopped, and bioassays of urine concentrates and RIA's of serum were used to monitor remission. Despite the fact that the patient was continuously receiving an oral contraceptive preparation, a significant level of biologically active gonadotropin was detected in the urine from January 10 to 20, 1975, but since HCG was not detected by serum RIA no further therapy was given. In May, 1975, both serum and urine assays showed high levels of HCG, and chemotherapy was reinstituted.

S. G., a 25-year-old white woman, gravida 1, para 0, molar pregnancy 1, had dilatation and curettage, in 1971, for a hydatidiform mole. The patient did well until February, 1974, when she underwent thoracotomy for a solitary lung nodule. The pathologic diagnosis was choriocarcinoma. The patient, while receiving oral contraceptive pills,* had multiple courses of actinomycin D or methotrexate without permanent remission. Part of the patient's clinical course is shown in Fig. 2. During the period from March 25 to April 24, 1975, three courses of actinomycin D were given, and both assays showed a progressive decrease in HCG to undetectable levels. However, during continued follow-up, the bioassay of urinary concentrates became

*Demulen 1/50, G. D. Searle & Co., P. O. Box 5110, Chicago, Illinois 60680.

*Ortho-Novum 1/50, Ortho Pharm. Corp., Route 202, Raritan, New Jersey 08869.

abnormal two weeks before HCG was detected in the serum. Chemotherapy was reinstituted when both assays became positive.

Comment

The gonadotropin responsible for biological activity in the urine concentrates, at a time when the serum RIA was negative, was shown to be HCG by a new RIA specific for this hormone in urinary extracts.[4] The assay, to be described in detail elsewhere, employs an antiserum produced in rabbits immunized with a tryptic peptide containing 23 of the 28 to 30 final amino acid residues unique to the carboxy-terminal segment of the HCG–beta subunit. With this assay, the urine of M. Y. Y. from January 15 to 20, 1975, had 6.5 to 11 I.U. of HCG per 24 hours. The urine of S. G., from May 15 to 25, 1975, had 5.4 to 6.6 I.U. per 24 hours. A normal value is less than 1.5 I.U. per 24 hours. The urinary RIA confirms the presence of HCG at a time when the serum RIA was unable to detect HCG.

Although the serum HCG–beta-subunit RIA has been used successfully in the management of trophoblastic disease, studies of these two patients show that viable trophoblastic tissue may persist after HCG becomes undetectable by this assay. Furthermore, results in these two patients point to the usefulness of assays for HCG in urine concentrates for the detection of persistent viable trophoblastic tissue in women at risk for gestational trophoblastic neoplasms.

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Glucagon secretion in late pregnancy and the puerperium

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S. S. C. YEN
La Jolla, California

Fasting plasma glucagon levels in late pregnancy were not significantly changed from those of nonpregnant matched control subjects, but at 6 to 8 weeks post partum a significant decrease in fasting glucagon levels was observed. Acute elevation of plasma glucose levels (via 25 Gm. intravenous glucose loading) induced a suppression of glucagon levels. This glucose-mediated glucagon suppression appeared to be less during late pregnancy which is probably related to the smaller increments of plasma glucose following intravenous loading in late pregnancy as compared to postpartum values.

GLUCAGON IS A catabolic hormone with potent glycogenolytic, gluconeogenic, and lipolytic activities. These activities are precisely the opposite of those of insulin, and this bihormonal function is required for metabolic homeostasis.[1]

It has recently been emphasized that diabetes mellitus may be a disorder of an excess of glucagon secretion as well as impaired insulin release.[1–3] Since pregnancy represents a diabetogenic event, it would be important to evaluate glucagon secretion together with the well-established occurrence of hyperinsulinism during late pregnancy.[4] With the use of oral glucose loading, Daniel and associates[5] recently reported a more heightened suppression of plasma glucagon levels during late pregnancy than in the postpartum period. The present report describes the fasting levels of and the effect of intravenous glucose loading on plasma insulin and glucagon during late pregnancy and post partum in the same group of subjects.

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Research supported by Rockefeller Foundation Grant RF-75029. A portion of the patient studies was performed in the Clinical Research Center supported by National Institutes of Health Research Grant RR00827.

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Material and methods

Seven nonobese volunteer women, 21 to 26 years old, were studied during the 37 to 38 weeks of pregnancy (antepartum) and six to eight weeks after delivery (post partum); they served as their own controls. There was no family history of diabetes, and pregnancies and deliveries were uncomplicated. Except for ferrous sulfate and vitamins, they received no medication. All subjects reported to the Ambulatory Clinical Research Unit between 0830 and 0900 after an overnight fast and were placed at bed rest. A No. 18 gauge polyethylene cannula was placed in an antecubital vein for sampling and kept open with a slow drip of normal saline. Blood samples were collected five minutes before and at seven, 12, 17, 32, 47, and 62 minutes after intravenous glucose loading in the opposite arm (25 Gm., 50 per cent solution, over a period of two minutes). In addition, morning fasting plasma glucagon, insulin, and glucose concentrations were determined in seven nonpregnant, age- and weight-matched control subjects to serve as a comparison to values found during late pregnancy and postpartum periods.

Plasma insulin and glucagon concentrations were determined by radioimmunoassay methods previously described.[6–8] Unger's[1] 30-K glucagon antibody was used. All samples were measured in the same assays. Plasma glucose was measured by a ferricyanide reduc-

tion method with an AutoAnalyzer.* The K-value for the glucose disappearance rate was calculated by the method of least squares from the log-transformed plasma glucose values.[9] Paired and unpaired Student's t tests were used for statistical analyses.

Results

The mean (±standard error) fasting levels of insulin and glucagon during pregnancy were significantly higher than the postpartum control values while glucose concentrations were significantly lower (Fig. 1). However, the fasting plasma glucagon levels in late pregnancy were comparable to those found in nonpregnant, age- and weight-matched control subjects (137 ± 5.2 versus 126 ± 6.1 pg. per milliliter).

Following the intravenous glucose challenge, the plasma glucose achieved a higher level after birth than before birth, and the insulin response was reversed. Plasma glucagon levels displayed a significant decline during both antepartum and postpartum tests, but the antepartum higher basal levels of glucagon appear to have a lesser degree of suppression as compared to postpartum tests (Fig. 1). The rate of glucose disappearance (K-value) is not significantly different between antepartum (1.55 ± 0.11) and postpartum (1.42 ± 0.06) tests.

Comment

Under normal nonpregnant conditions, changes in the insulin profile are parallel to those of plasma glucose, but there is an inverse relationship between glucagon output and glucose concentrations.[1] If fasting glucagon levels are a function to prevent fasting hypoglycemia, an inappropriate glucose-glucagon interrelationship occurs during late pregnancy and at six to eight weeks post partum; despite a significantly lowered fasting plasma glucose concentration in late pregnancy, the fasting glucagon levels are not significantly different from those of nonpregnant matched control subjects (Fig. 1). Moreover, when the relative hyperinsulinism and the hypoglycemia returned to the nonpregnant range at six to eight weeks post partum, a paradoxical decline in fasting glucagon levels was found (Fig. 1). These findings are in agreement with the observation made by Daniel and associates.[5] The mechanism(s) and the physiologic role for such a modification during pregnancy and puerperium are unknown.

In nonpregnant subjects, acute elevation of plasma glucose concentrations by intravenous glucose loading

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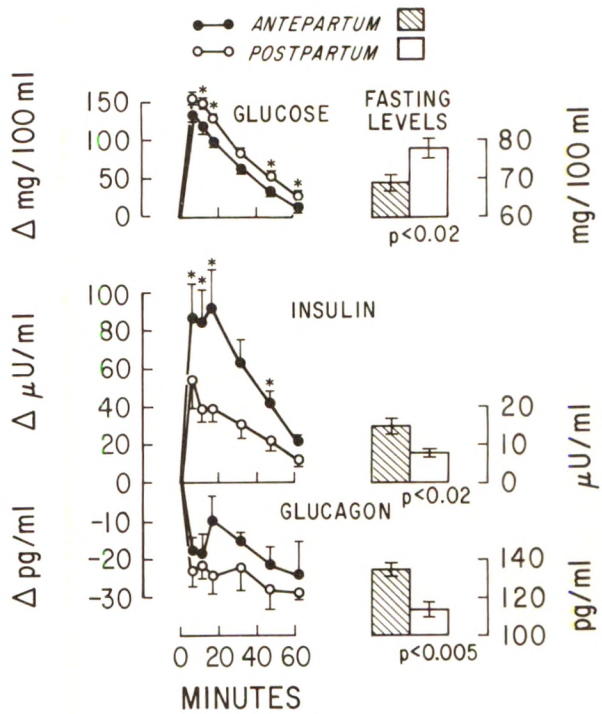


Fig. 1. Effects of intravenous glucose loading (25 Gm.) on Δ plasma glucose, insulin, and glucagon concentrations studied sequentially during the antepartum period (37 to 38 weeks) and post partum (six to eight weeks) in a group of nonobese normal pregnant women. The fasting levels for plasma glucose, insulin, and glucagon determined during antepartum and postpartum periods are also shown. *Denotes a significant difference between antepartum and postpartum values at $P < 0.05$ or greater as analyzed by the paired t test.

(25 Gm.) induces a rapid suppression of glucagon levels with a net decrease of 20 to 30 pg. per milliliter.[7] This relationship between plasma glucose and glucagon appears to be maintained during late pregnancy as well as in the puerperium (Fig. 1). However, a lesser degree of glucagon suppression in response to acute elevation of plasma glucose was found in antepartum tests than in postpartum tests, although the difference was not statistically significant. This relative difference in glucose-mediated glucagon suppression between the antepartum and postpartum states is likely due to a significantly smaller elevation of plasma glucose in response to the same glucose load before delivery as compared to after delivery (Fig. 1). In this regard, Daniel and associates,[5] using oral glucose loading (100 Gm.), found just the opposite; elevation of plasma glucose levels was higher and the glucagon suppression was greater during the antepartum tests than during postpartum tests. Taken together, these findings suggest that a dose-related inhibition of glucagon release by circulating glucose levels appears to be

operative during pregnancy. Studies to define further the relationship between metabolic fuel and glucagon secretion in normal and diabetic pregnancies are underway.

We wish to acknowledge the excellent technical assistance provided by M. Sigel and J. Aurand.

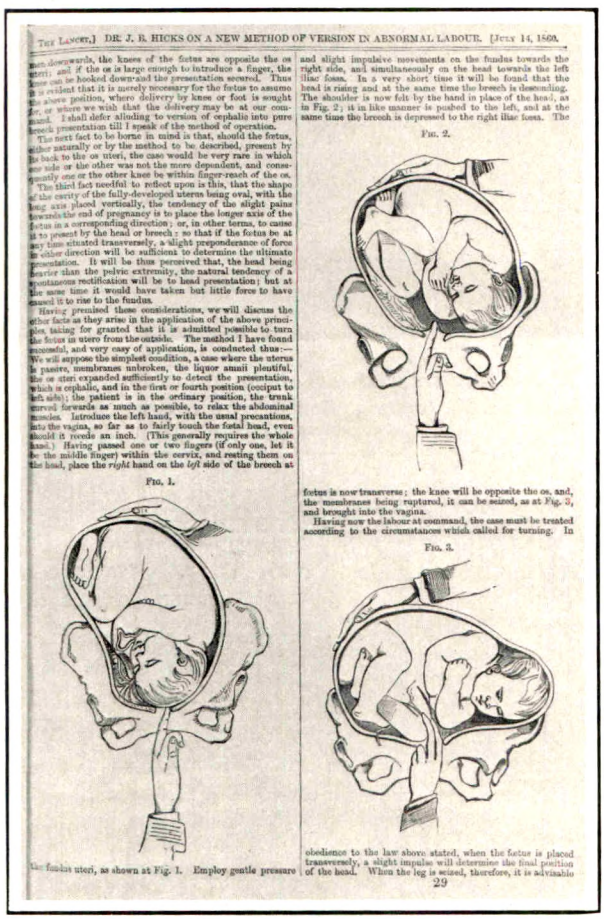
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Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

On a new method of version in abnormal labour

JOHN BRAXTON HICKS
The Lancet, vol. 2, pp. 28-30 and 55, 1860



THE LANCET.] DR. J. B. HICKS ON A NEW METHOD OF VERSION IN ABNORMAL LABOUR. [JULY 14, 1860.

...men downwards, the knees of the fœtus are opposite the os uteri; and if the os is large enough to introduce a finger, the knee can be hooked down and the presentation secured. Thus it is evident that it is merely necessary for the fœtus to assume the above position, where delivery by knee or foot is sought for, or where we wish that the delivery may be at our command. I shall defer alluding to version of cephalic into pure breech presentation till I speak of the method of operation.

The next fact to be borne in mind is that, should the fœtus, either naturally or by the method to be described, present by its back to the os uteri, the case would be very rare in which one side or the other was not the more dependent, and consequently one or the other knee be within finger-reach of the os.

The third fact needful to reflect upon is this, that the shape of the cavity of the fully-developed uterus being oval, with the long axis placed vertically, the tendency of the slight pains towards the end of pregnancy is to place the longer axis of the fœtus in a corresponding direction; or, in other terms, to cause it to present by the head or breech; so that if the fœtus be at any time situated transversely, a slight preponderance of force in either direction will be sufficient to determine the ultimate presentation. It will be thus perceived that, the head being heavier than the pelvic extremity, the natural tendency of a spontaneous rectification will be to head presentation; but at the same time it would have taken but little force to have caused it to rise to the fundus.

Having premised these considerations, we will discuss the other facts as they arise in the application of the above principles, taking for granted that it is admitted possible to turn the fœtus in utero from the outside. The method I have found successful, and very easy of application, is conducted thus:—We will suppose the simplest condition, a case where the uterus is passive, membranes unbroken, the liquor amnii plentiful, the os uteri expanded sufficiently to detect the presentation, which is cephalic, and in the first or fourth position (occiput to left side); the patient is in the ordinary position, the trunk curved forwards as much as possible, to relax the abdominal muscles. Introduce the left hand, with the usual precautions, into the vagina, so far as to fairly touch the fœtal head, even should it recede an inch. (This generally requires the whole hand.) Having passed one or two fingers (if only one, let it be the middle finger) within the cervix, and resting them on the head, place the *right* hand on the *left* side of the breech at

FIG. 1.

the fundus uteri, as shown at Fig. 1. Employ gentle pressure and slight impulsive movements on the fundus towards the right side, and simultaneously on the head towards the left iliac fossa. In a very short time it will be found that the head is rising and at the same time the breech is descending. The shoulder is now felt by the hand in place of the head, as in Fig. 2; it in like manner is pushed to the left, and at the same time the breech is depressed to the right iliac fossa. The

FIG. 2.

fœtus is now transverse; the knee will be opposite the os, and, the membranes being ruptured, it can be seized, as at Fig. 3, and brought into the vagina.

Having now the labour at command, the case must be treated according to the circumstances which called for turning. In

FIG. 3.

obedience to the law above stated, when the fœtus is placed transversely, a slight impulse will determine the final position of the head. When the leg is seized, therefore, it is advisable

Hicks, physician and accoucheur at Guy's Hospital, was one of the nineteenth century pioneers in obstetrics. In this, his first account of combined internal and external podalic version, he introduced a great improvement over the then used methods of version, either internal podalic or the less often used external. Hicks' method (see text at left) was to introduce one or two fingers of the left hand into the cervix; with the right hand pressing on the breech, slowly turn the fetus; and by grasping a knee, bring the leg into the vagina. Hicks considered the advantages of this approach, "Still, if it can be shown that in a considerable number of cases requiring version, the operation can be accomplished as quickly, or even more so, without the necessity of introducing the hand into the uterus, with the exception of one or two fingers passed a little way into the os, I am sure that such a modification of this more or less hazardous operation will recommend itself without any panegyric on my part. For in that case it will readily be perceived that we shall avoid—1. The addition of the hand, and perhaps arm, to the uterine contents; and the irritation, present and future, caused by it. 2. Entry of air within the uterine cavity. 3. Liability to rupture of uterus. 4. Much of the pain and distress felt in the ordinary plan. 5. The removal of the coat, and baring the arm of the operator; and, as a minor consideration, 6. The fatigue and pain endured by the operator while the hand is in utero." Hicks considered the procedure of value in cases of partial or even complete placenta previa, malpresentation, and eclampsia. He concluded with a report of five cases of placenta previa in which three of the mothers and one infant survived. He noted, "As soon as the finger can enter the os, it is practicable to bring down the knee or foot, and by that means have the command of the haemorrhage and labour at the same time. . . ." He later reported 15 additional cases where this method was employed. They included cases of abruptio placentae, eclampsia, pelvic contraction, transverse lie, prolapsed cord, etc. (Trans. Obstet. Soc. Lond. 5: 219, 1864). The adoption of Hicks' method of version reduced the mortality rate associated with placenta previa from about 30 to 5 per cent. Marmaduke B. Wright, of Cincinnati, introduced combined external and internal cephalic version six years earlier (Ohio State Med. Soc. Trans. 9: 59, 1854). It is to Braxton Hicks, however, that credit must be given for inventing and popularizing this method of combined podalic version.

CURRENT DEVELOPMENTS

The androgenic polycystic ovary

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The polycystic ovary has the capacity to produce excessive androgens (Δ^4-androstenedione, dehydroepiandrosterone, and testosterone). Whether this disorder is caused by constant pituitary priming of the ovaries due to hypothalamic-pituitary derangement or an ovarian enzyme defect, the end result is the same, i.e., abnormal androgen production. In an effort to explain the syndrome, we offer the hypothesis of an inherently sensitized adrenal secreting excessive androgen which leads to an imbalance in the hypothalamic-pituitary axis. The result is a tonic stimulation of the ovaries eventuating in "the androgenic polycystic ovary."

THE MYSTIQUE surrounding the polycystic ovary has beguiled gynecologists and endocrinologists for many years. When Galen (second century) designated the ovary as the female testicle, he, presciently, served notice that the female gonad was not unlike a testis. The large pale ovary, a descriptive term employed by Albright for the polycystic ovary of Stein-Leventhal, indeed bears a semblance to the testicle. Such ovaries have the capacity to produce abnormal amounts of androgens so that the sobriquet "the androgenic ovary"* is not inappropriate.

The polycystic ovary was first alluded to by Chéreau, in 1844, when he described sclerocystic ovaries. A host of conditions was attributed to them, and later in the century oophorectomy became a widely used therapeutic procedure. In 1896, Waldo[1] applied the principle of partial resection rather than extirpation. Several years later, Findley,[2] in discussing cystic degeneration of the ovary, stated that wedge resection was of great value; nonetheless, he did not hesitate to remove both ovaries. Forgue and Massabuau[3] (1910) reviewed the subject of sclerocystic ovaries and perhaps suggested the more appropriate name "microcystic ovaries" and concluded, " . . . que l'on connait mal les lésions anatomiques précises de l'ovaire a petits kystes." In 1935, Stein and Leventhal[4] reported on a series of cases of amenorrhea and bilaterally enlarged polycystic ovaries. The correlation of the symptomatology, means of diagnosis, and wedge resection as the ideal mode of therapy established the syndrome which bears their names.

From the Department of Endocrinology, Medical College of Georgia.

Special University Lecture on "The Polycystic Ovary," delivered at Middlesex Hospital Medical School, London, England, November 28, 1974.

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**A sometime term employed by H. Simmer and also by R. V. Short.*

Histopathology

Is there a specific pathology for the polycystic ovary? In general, the gross appearance of the polycystic ovary is not specific, for a similar picture may be seen in other conditions associated with anovulation such as Cushing's syndrome, congenital adrenal hyperplasia, hypothyroidism, and acromegaly.

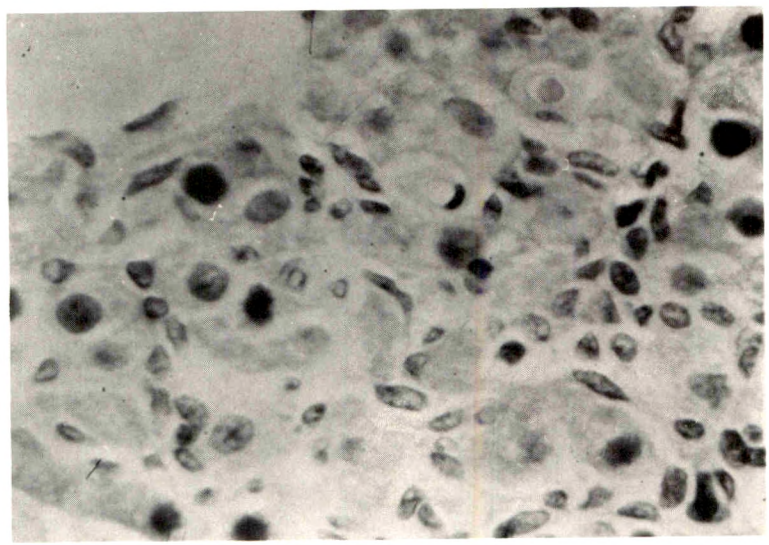


Fig. 1. Photomicrograph of histologic section of ovary from a case of virilism and large pale ovaries. Found in ovarian medulla were "androgenic cells"—large cells with vesicular nuclei and prominent nucleoli. (From Greenblatt, R. B., and McDonough, P. G.: The Ovary, Springfield, Illinois, 1969, Charles C Thomas, Publisher, p. 12.)

The gross appearance of the polycystic ovary is quite characteristic. It is usually elongated, one and a half to two times normal, with a smooth, pearly white capsule or tunica. In some instances, the ovary is not significantly enlarged. On sectioning, numerous pea-sized cysts, filled with clear fluid, occupy the thickened cortex. Microscopically, the cysts may be devoid of a granulosa cell lining while many others are lined by one or more layers of granulosa cells. Distinctive, however, is the marked hyperplasia of the theca interna. The theca externa may show proliferation with occasional mitotic figures. Stromal hyperplasia is quite frequently observed, but the presence of individual "androgenic" cells (Fig. 1) or nests of luteinized stroma-theca cells (Fig. 2) are quite specific for the polycystic ovary, especially when associated with marked hirsutism.[5] Indirect evidence of hormonal activity may be assumed in that these cells, as well as the theca interna, are lipid laden and rich in glucose-6-phosphate dehydrogenase.[6] The cortex is often fibrotic and the capsule is thickened. The question has often been asked, "is the thick sclerotic capsule a deterrent to the ovulatory process?"

The myth that the thick sclerotic tunica acts as a mechanical barrier to ovulation is perpetuated in many textbooks. The distinguished Viennese gynecologist, Prof. Antoine,[7] as recently as 1971, wrote that among the causes of infertility, " . . . there may be anatomical reasons like in the Stein-Leventhal syndrome with its thickened tunica albuginea." For this reason, operations for stripping the capsule or techniques for ovarian eversion were devised.[8] Some believe that ovulation takes place after wedge resection along the weakened approximate edges of the ovary.[9] One of us (R. B. G.) performed unilateral oophorectomy in five patients with the classical syndrome, resulting in cyclic ovulations from the contralateral ovary despite its thickened capsule.[10] Since clomiphene, human gonadotropins, and glucocorticoids may readily induce ovulation, the thick capsule may no longer be considered a deterrent to ovulation.

Hypothalamic-pituitary axis and the polycystic ovary. Is the polycystic ovary primarily a hypothalamic-pituitary disorder? Women with this syndrome occasionally ovulate under stress conditions. This was strikingly brought to the fore when, in 1958, a 32-year-old woman with classical Stein-Leventhal syndrome was hospitalized for wedge resection in the hope of resolving her infertility problem. At the time of admission, she was nine months amenorrheic. Previous studies revealed elevated urinary 17-ketosteroids, low urinary hydroxycorticoids, and normal urinary gonadotropins. Laparotomy revealed typically elongated ovaries with a thick pearllike capsule and a small fresh corpus luteum bulging the lateral extremity of the left ovary. Wedge resection was performed on each ovary. The histopathology was in consonance with that usually found, except for the fresh corpus luteum and an old hyalinized corpus albicans in one of the sections from the right ovary. Incidentally, the patient has had regular ovulatory menses for the 16 years since operation.[10]

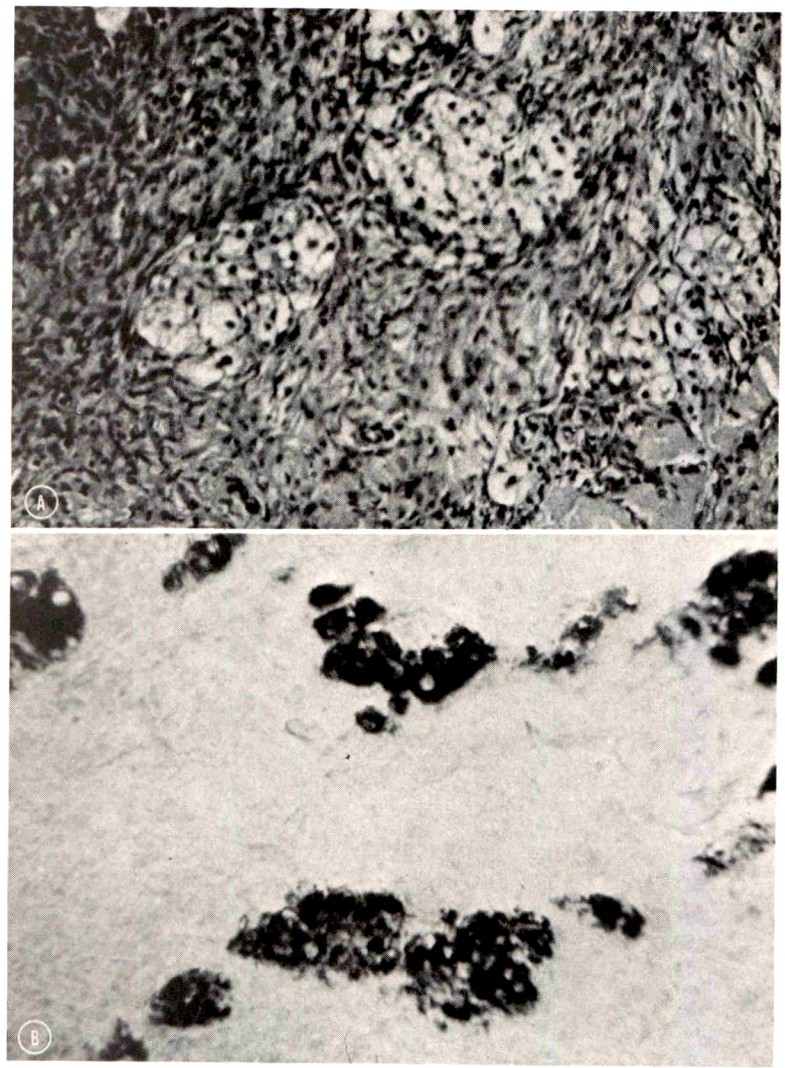


Fig. 2. Top, Photomicrograph of histologic section of ovary from a hirsute patient with polycystic ovaries. Bottom, Sudan III stain shows rich lipid content of the luteinized, large, pale, polyhedral stromal cells seen in *A*. (From Greenblatt, R. B., and McDonough, P. G.: The Ovary, Springfield, Illinois, 1969, Charles C Thomas, Publisher, p. 11.)

Support for spontaneous ovulations in stress situations was obtained in our study of 30 oligomenorrheic or amenorrheic women hospitalized with Stein-Leventhal syndrome. Five ovulated before clomiphene therapy or wedge resection could be undertaken. In one case, on the morning of admission, both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values were at levels compatible with the ovulatory surge.[11]

Human pituitary gonadotropins were administered to a normal woman for four consecutive days before laparotomy. A wedge of ovarian tissue was obtained and assayed for steroid content—Δ^4-androstenedione was more than tenfold greater than that of normal control subjects (Fig. 3) and similar to levels found in patients with polycystic ovaries.[12]

When luteinizing-releasing factor (LRF) was administered to women with typical Stein-Leventhal syndrome, the LH response was good, and the FSH response was poor. This pattern was similar to that obtained in the early follicular phase of normal women and in other oligomenorrheic women (Figs. 4A and 4B).

Typical polycystic ovaries may be found in the presence of a virilizing adrenal adenoma[13] and in the contralateral ovary in women harboring an ovarian androgen-producing tumor.[14]

One may conclude from the above four sets of

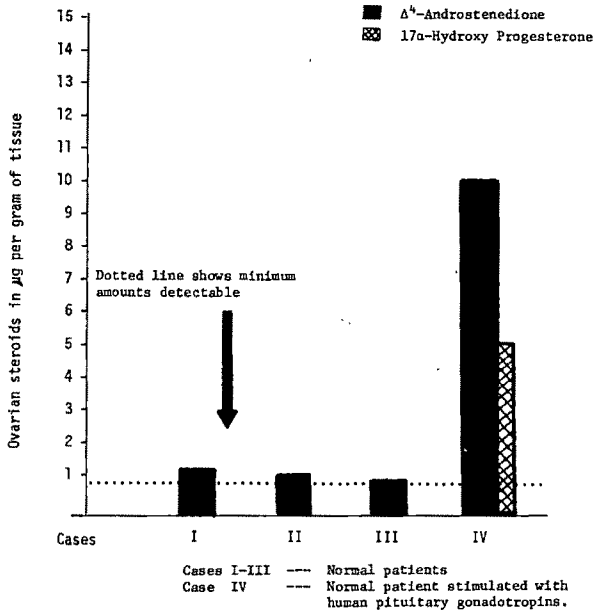


Fig. 3. Wedges of ovarian tissue were obtained at laparotomy from four normal women. Homogenates yielded very low values for Δ^4-androstenedione, but there was a tenfold increase after four days of stimulation with human pituitary gonadotropins. (From Greenblatt, R. B., and Mahesh, V. B.: J. Reprod. Med. **13**: 86, 1974.)

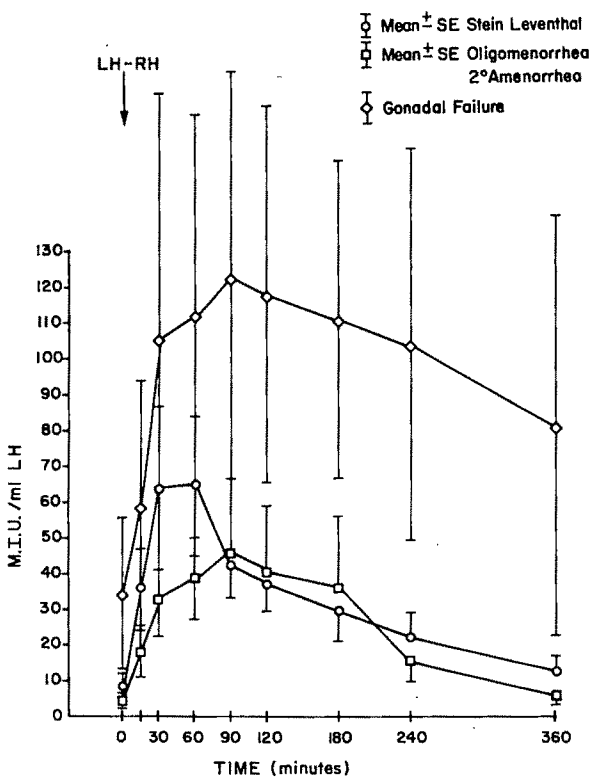


Fig. 4A. LH and FSH response to LH-RH (LRF) in Stein-Leventhal syndrome as compared to gonadal failure and amenorrhea.

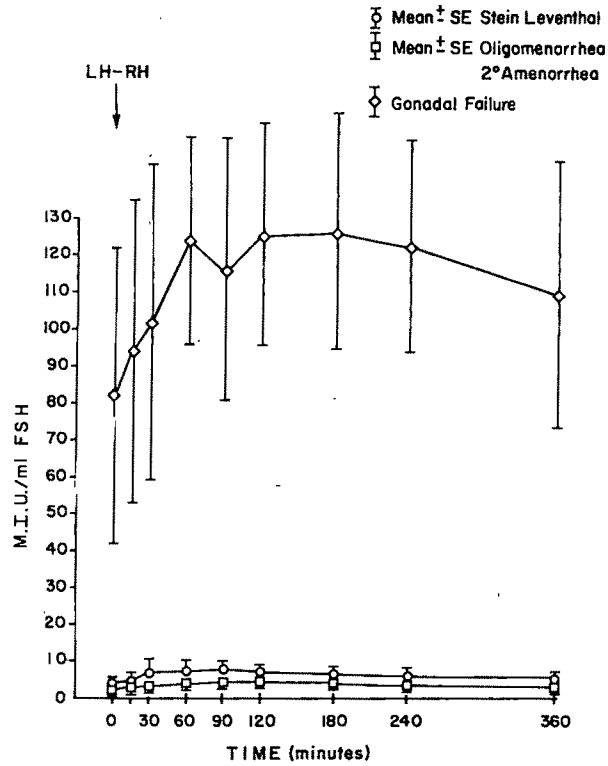


Fig. 4B. LH and FSH response to LH-RH (LRF) in Stein-Leventhal syndrome as compared to gonadal failure and amenorrhea.

observations that the pituitary-ovarian axis remains more or less intact in the polycystic ovary. Endogenous androgens in certain virilizing syndromes have a direct or indirect effect on the ovary. Excess androgens appear to affect the higher brain centers of the hypothalamus, resulting in a tonic rather than a rhythmic stimulation of the ovaries by gonadotropins.

The polycystic ovary as a source of excessive androgens

Early reports of elevated urinary 17-ketosteroids in the polycystic ovary syndrome invariably implicated the adrenal as the main source of excessive androgens.[15–21] The possibility of the secretion of excessive androgens by the polycystic ovary was considered by one of us (R.B.G.) as early as 1953,[22] by the demonstration of a decrease in 17-ketosteroids after wedge resection or following extirpation of the ovaries. Similar findings were made in later years by other investigators.[18, 20, 23–27] However, wedge resection failed to induce ovulatory menses in occasional patients despite a lowering of urinary 17-ketosteroids; yet ovulation could be induced by the administration of glucocorticoids in these same patients.[22] The adrenal

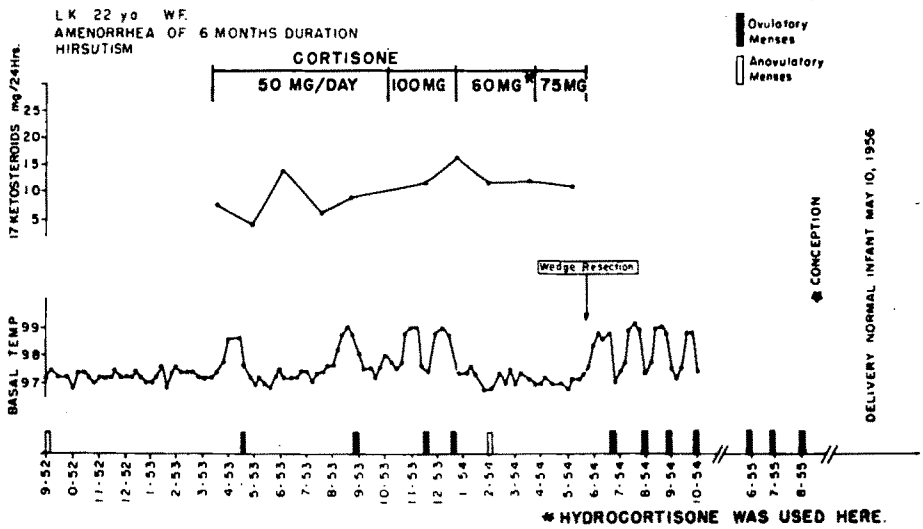


Fig. 5. Patient L. K. Note sporadic ovulations after cortisone and the establishment of regular ovulatory menses following wedge resection. (From Greenblatt, R. B.: The Hirsute Female, Springfield, Illinois, 1963, Charles C Thomas, Publisher, chap. 9. p.158.)

component could not be overlooked. Extensive studies were undertaken in our laboratory to establish the source of excessive androgens in the polycystic ovary syndrome.[28–36] Fractionation and individual estimation of various urinary steroids showed that the majority of patients with this syndrome had elevation in the 11-oxygenated-17-ketosteroid or the 11-deoxy-17-ketosteroid fraction or both. The polycystic ovary syndrome complex with excessive androgens could represent an adrenal or an ovarian disorder or one involving both. Thus, corticosteroid therapy might induce ovulatory menses, while wedge resection could do likewise in the same patient (Fig. 5).

Confirmation of excessive secretion of androgens by the polycystic ovaries with other studies. In the 1960's, the secretion of excessive androgens by the polycystic ovary was a new concept; therefore, adequate confirmation was needed. This was done by the study of the steroid content of ovarian tissue and ovarian venous blood.

The normal ovary contained only small quantities of Δ^4-androstenedione. The ovaries of patients with the polycystic ovary syndrome contained large quantities of either Δ^4-androstenedione and 17α-hydroxyprogesterone and/or dehydroepiandrosterone.[30, 32] The isolation of dehydroepiandrosterone from polycystic ovaries has been confirmed by Starka and associates[37] and Baulieu and colleagues.[25] Large quantities of Δ^4-androstenedione have been isolated from ovarian follicular fluid by Short and London[38] and Mahajan and co-workers.[39] The isolation of dehydroepiandrosterone from the polycystic ovaries of Stein-Leventhal syndrome and of 17α-hydroxy-Δ^5-pregnenolone with larger quantities of dehydroepiandrosterone following the in vivo stimulation of such ovaries with human pituitary FSH indicates that dehydroepiandrosterone is probably synthesized from cholesterol via Δ^5-pregnenolone and 17α-hydroxy-Δ^5-pregnenolone. In vitro incubation studies with radioactive Δ^4-androstenedione and dehydroepiandrosterone suggest that polycystic ovaries have abnormalities in the aromatization of either Δ^4-androstenedione or ovarian 3β-*ol*-dehydrogenase. Enzymatic abnormalities in polycystic ovaries have also been suggested by several workers, and the subject has been reviewed by Mahesh and Greenblatt.[32] The secretion of large quantities of Δ^4-androstenedione and dehydroepiandrosterone by the polycystic ovary was amply confirmed by the isolation of large quantities of these compounds from ovarian venous blood.[30]

Gonadotropin secretion in the polycystic ovary syndrome

The initial work on the secretion of gonadotropins in the polycystic ovary syndrome was done by urinary assays. The findings of several investigators showed normal levels of FSH and normal to elevated levels of LH. The relative insensitivity of the urinary methods, the need for large quantities of urine, and the presence of interfering material prevented precise evaluation of the alterations in gonadotropin secretion. The development of radioimmunoassays for serum FSH and

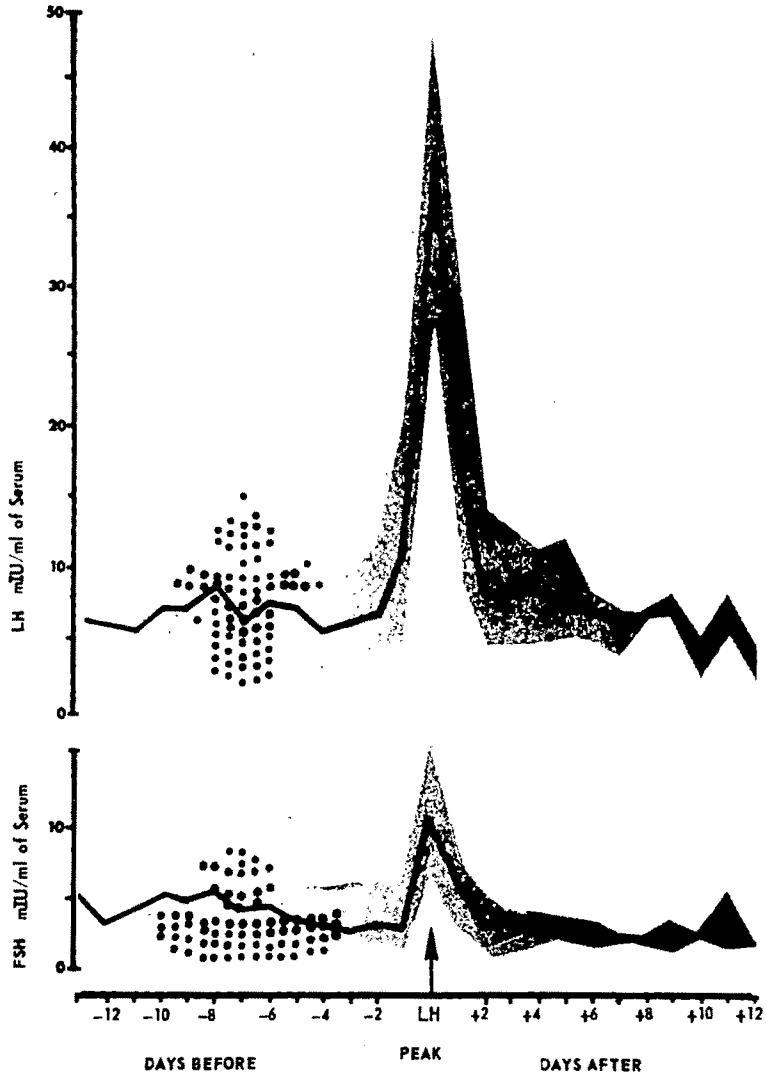


Fig. 6. Daily serum FSH and LH values in six patients with Stein-Leventhal syndrome obtained during an amenorrheic phase, indicated by dots. These are compared to serum gonadotropins during the menstrual cycle of eight normal ovulating subjects. The mean is shown by the solid lines; the range is depicted by the shaded area. (From Gambrell, R. D., Greenblatt, R. B., and Mahesh, V. B.: Obstet. Gynecol. **42:** 433, 1973.)

LH has now made it possible to study the patterns in patients with normal cyclic menses and in those with ovulatory failure.

Studies of serum gonadotropin levels in patients with the polycystic ovary syndrome in our laboratory showed that LH may be low, normal, or elevated with sporadic peaks (Fig. 6).[40] Serum FSH levels were, in general, lower than those found in the follicular phase of the normal menstrual cycle. The ovulatory surge of both FSH and LH was absent. Extensive work has been done by our group in the induction of ovulation with clomiphene citrate in patients with the polycystic ovary syndrome.[11] It has been adequately demonstrated that clomiphene brings about the release of gonadotropins, resulting in ovulation. Patients with the polycystic ovary syndrome varied in their response to clomiphene, some showing very little change in the gonadotropin secretion pattern and lack of ovulation. Others showed a dramatic surge of LH similar to that observed in the normal menstrual cycle but with very little or no change in FSH, and these patients also did not ovulate. The patients who ovulated as a result of clomiphene treatment showed a peak in urinary estrogens, followed by a surge of both FSH and LH (Fig. 7). These

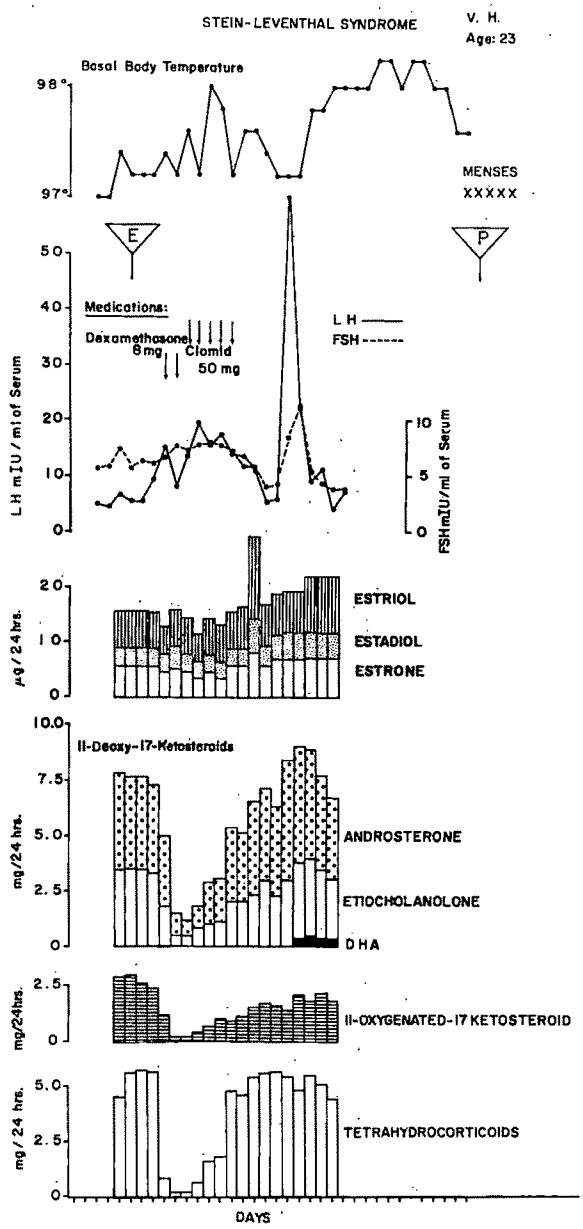


Fig. 7. Patient V. H. Ovulation induced by clomiphene therapy in a 23-year-old married nulligravid woman who gave a history of increasing hirsutism of five years' duration. Note estrogen peaks followed by LH and FSH surge. (*E* = Proliferative endometrium; *P* = secretory endometrium.) (From Gambrell, R. D., Greenblatt, R. B., and Mahesh, V. B.: Obstet. Gynecol. **38**: 853, 1971.)

results indicate that, even in the human subject, FSH may have significance in the rupture of the follicle and ovulation. It may be of interest to note in this regard that Strott and associates[41] observed that in patients with a short luteal phase the only consistent deviation from the normal was a dulled or misplaced FSH peak near the time of ovulation.

Measurement of blood androgens

The measurement of various androgens in the blood of hirsute patients with the polycystic ovary syndrome was carried out by several investigators with emphasis on testosterone measurements.[42–46] Although in a large number of cases blood testosterone was elevated, nevertheless, it was found to be within normal limits in a substantial number of hirsute patients. By the use of steroid-specific antisera and chromatographic techniques, we have recently developed a method for multiple steroid radioimmunoassay in our laboratory.[47] With the use of this method, hirsute patients were found to have significant elevations in not only testosterone but also dehydroepiandrosterone, Δ^4-androstenedione, 5α-dihydrotestosterone and 17α-hydroxyprogesterone (Fig. 8). The elevation in these steroids is in agreement with the variety of steroids isolated from ovarian tissue and ovarian venous blood.

Studies of adrenal and ovarian vein blood steroids to determine the source of excessive androgens

Studies of peripheral blood steroids and urinary steroids have yielded valuable information regarding excessive androgen secretion in the polycystic ovary syndrome. However, whether the source of these androgens was the adrenal or the ovary has often been difficult to ascertain.

A method of selective adrenal and ovarian vein catheterization was developed by Jacobs[48] and applied by Kirchner and Jacobs[49] and in our department by Stahl and colleagues,[50] in an attempt to determine the source(s) of testosterone in hirsute women. Before such a procedure can be recommended, one would have to establish whether the stress of the procedure would modify adrenal and/or ovarian steroidogenesis. Moreover, in view of the pulsatile and episodic secretion of adrenal steroids and perhaps even ovarian steroids, one would have to determine whether the sampling over a short period of time would accurately reflect such secretion. Furthermore, as it is more difficult to obtain right ovarian and adrenal vein samples, would the samples from the left adrenal and ovary be representative? Finally, would it be possible to magnify further the secretion of androgens by challenging the ovary with an intravenous injection of human chorionic gonadotropin (HCG)? In an attempt to answer some of these questions, a study of adrenal and ovarian vein blood steroids was carried out in a number of hirsute women before and after administration of HCG and in one woman before and after administration of adrenocorticotropic hormone (ACTH).[51]

Effect of HCG on ovarian and adrenal steroid

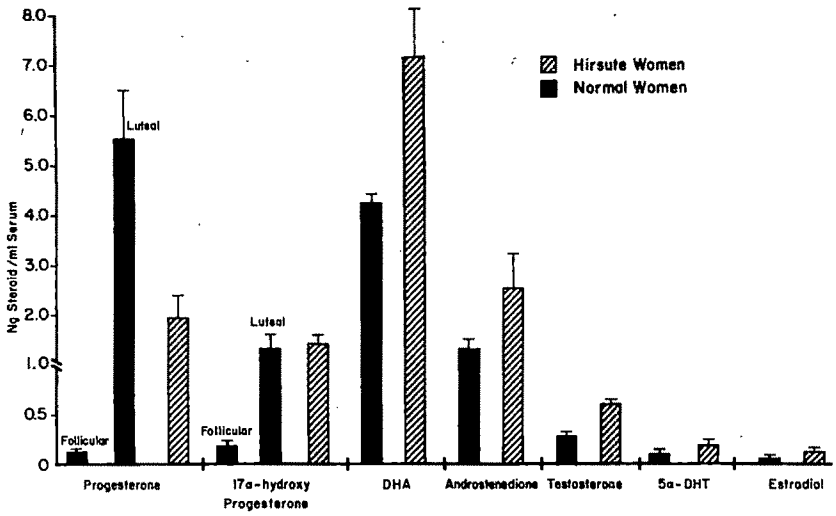


Fig. 8. Peripheral blood steroid levels in 10 normal women and 13 hirsute women. Note elevation of dehydroepiandrosterone, Δ^4-androstenedione, and testosterone in hirsute women. Levels of 17α-hydroxyprogesterone and progesterone levels in hirsute women were comparable to those found in the luteal phase of normal women.

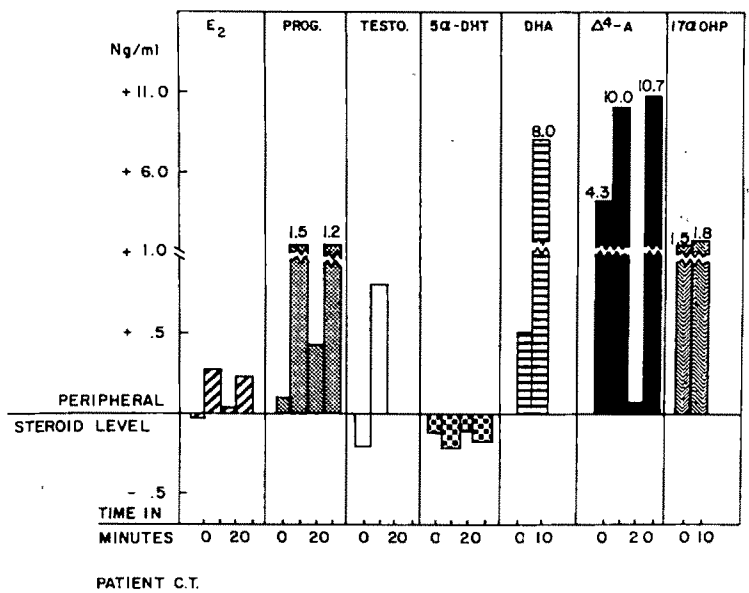


Fig. 9. Note dramatic increases in estradiol, progesterone, and Δ^4-androstenedione in the blood from the left ovarian vein 10 and 30 minutes after administration of 2,000 I.U. of HCG. Similar increases were found in testosterone and DHA 10 minutes after HCG.

secretion. Patient C. T., who was amenorrheic and diagnosed as having Stein-Leventhal syndrome, was treated with 2,000 I.U. of HCG. Prior to the HCG infusion, peripheral concentrations (Fig. 9) to dehydroepiandrosterone (DHA), androstenedione, and testosterone were markedly elevated as compared to those of nonhirsute women. Progesterone concentrations were comparable to those found in the follicular phase, but 17α-hydroxyprogesterone was much higher than normal follicular phase concentrations. HCG administration brought about a dramatic increase in all steroids by 10 minutes, followed by a fall at 20 minutes and a further rise at 30 minutes in peripheral samples. These changes in peripheral blood were due to the obvious ovarian stimulation at 10 and 30 minutes after HCG. Changes in adrenal vein steroid levels as

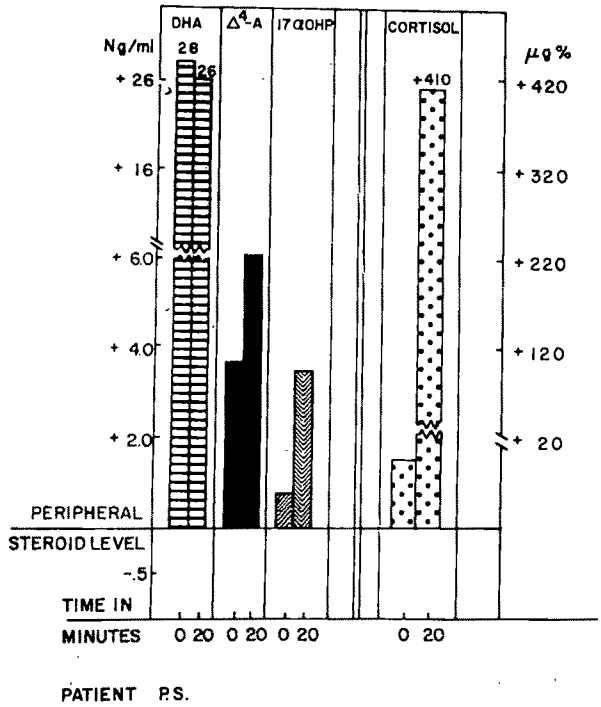


Fig. 10. Note dramatic increase in DHA, Δ^4-androstenedione, 17α-hydroxyprogesterone, and cortisol in adrenal vein blood after 40 I.U. of ACTH.

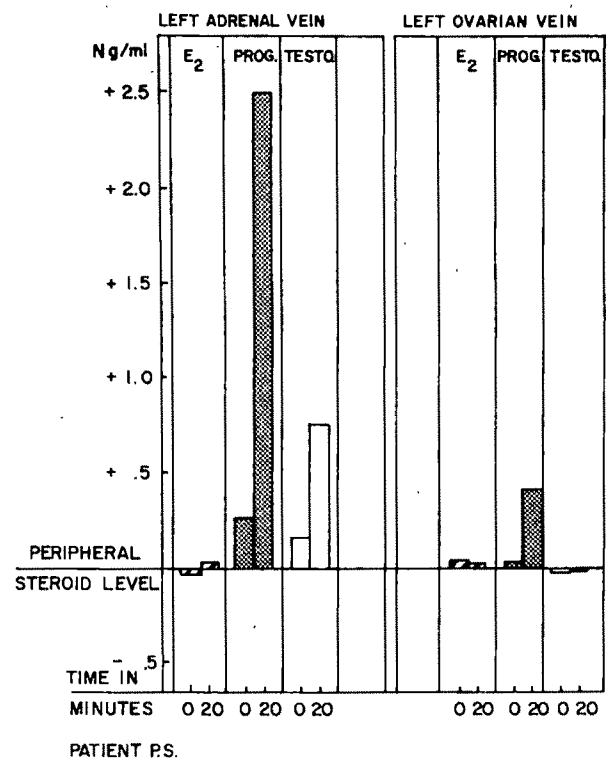


Fig. 11. ACTH (40 I.U.) also caused a marked increase in progesterone and testosterone in adrenal vein blood. However, changes occuring in ovarian vein blood were absent or minimal.

compared to peripheral levels were minimal and indicated no action of HCG on adrenal function.

Effect of ACTH on ovarian and adrenal steroid secretion. Patient P. S., on Day 7 of the menstrual cycle, was given 40 I.U. of ACTH intravenously to evaluate its effect on ovarian steroid secretion. This procedure was utilized to help evaluate the acute effect of stress on ovarian function. As shown in Figs. 10 and 11, marked adrenal stimulation occurred within 20 minutes as compared to the control sampling. Increased secretion of progesterone, testosterone, Δ^4-androstenedione, 17α-hydroxyprogesterone, and cortisol was evident in the adrenal vein blood samples; however, only small changes occurred in concentrations of ovarian vein steroids. These results suggest only minimal effects if any of ACTH on ovarian function.

Effect of HCG on the left ovary with the presence of a functional corpus luteum in the right ovary. Patient T. S., who was found at laparoscopy to have a corpus luteum of the right ovary, had peripheral control levels of progestins comparable with normal luteal phase concentrations. Peripheral concentrations of DHA and androstenedione were normal; however, testosterone concentrations were elevated. HCG treatment resulted in a progressive increase in all steroids assayed over the course of 30 minutes of sampling from the peripheral

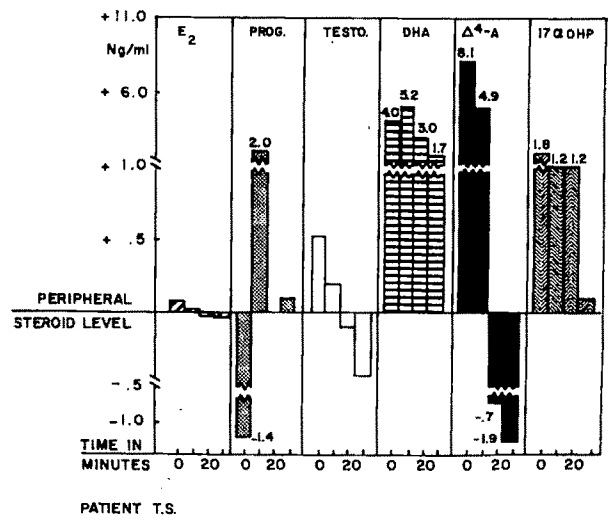


Fig. 12. Pattern of steroid secretion and response to HCG by the left ovary in a patient with a functional corpus luteum in the right ovary. Note that, with the exception of a sporadic increase in progesterone, all other steroids showed a decrease after HCG. The decrease could be accounted for by increased levels of circulating peripheral steroids in all probability due to the effect of HCG on the contralateral ovary with the corpus luteum.

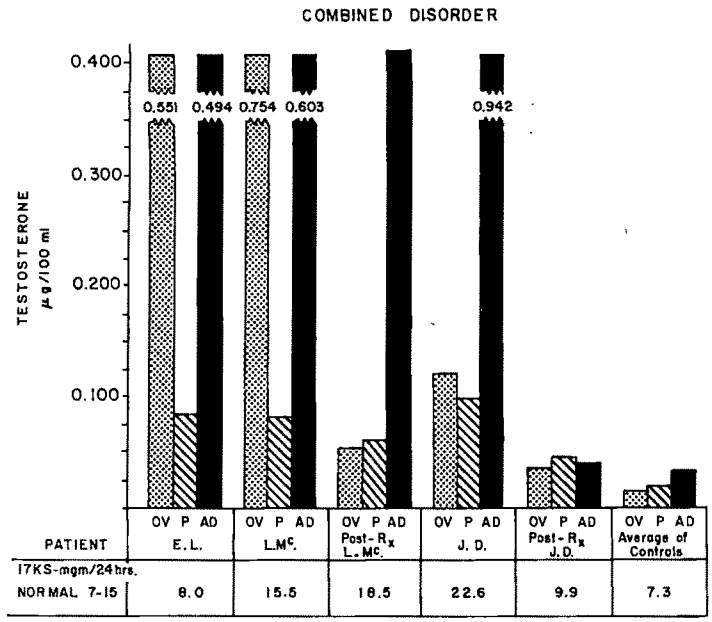


Fig. 13. Plasma testosterone values in three of eight hirsute patients with polycystic ovaries. In each patient, ovarian and adrenal vein testosterone obtained through femoral catheterization was higher than peripheral venous levels. In Patient L. Mc., estrogen therapy resulted in an ovarian and peripheral testosterone decrease to within normal limits while adrenal testosterone remained markedly elevated. Patient J. D. received estradiol pellets for ovarian suppression combined with prednisone therapy, 7.5 mg. every morning, resulting in testosterone reduction to values found in nonhirsute control subjects. (From Stahl, N. L., Teeslink, C. R., and Greenblatt, R. B.; AM. J. OBSTET. GYNECOL. **117:** 197, 1973.)

vein. Control sampling of the left ovarian vein revealed evidence for the secretion of substantial amounts of DHA and androstenedione, but there was no increase after HCG, which indicates a poor response by this ovary (Fig. 12). The decreasing quantities of estradiol, androstenedoine, testosterone, and 17α-hydroxyprogesterone in the left ovarian vein in relation to peripheral vein concentrations may indicate a reponse by the right ovary (containing a corpus luteum) to the HCG.

The authors believe that the technique of selective adrenal and ovarian venous cannulation does give direct information as to the source(s) of androgens in hirsute women, especially when the ovary is the source of excessive androgens. Adrenal values are difficult to interpret because of the pulsatile phenomenon and/or stress. In cases where the ovary is actively secreting androgens and other steroids, HCG treatment causes an acute increase in these compounds. The results of ovarian vein catheterization may be misleading if a corpus luteum is present in the contralateral ovary.

Role of androgens in causing ovulatory failure

Many theories have been advanced to explain the sequence of events resulting in the polycystic ovary syndrome. It is well established that excessive androgens are present in the majority of patients with the syndrome. This excessive secretion may be of adrenal or ovarian origin but more often is a combination of the two (Fig. 13). Inappropriate secretion of gonadotropins due to an aberration in the hypothalamic regulatory mechanism has often been suggested by researchers as the possible physiopathology of the syndrome.

We believe that the elevated level of circulating androgens in blood is the major factor responsible for ovulatory failure. Reduction of a part of the steroidogenic tissue by wedge resection of the ovary results in a lowering of circulating androgens—an observation now amply confirmed. Reduction of circulating androgens contributes significantly to resumption of cyclic ovulatory menses. Adrenal suppression, when the adrenal gland is the major source of androgen, often produces the desired results.

If, indeed, excessive androgens cause polycystic ovaries and ovulatory failure in the presence of otherwise seemingly normal adrenals and a normal hypothalamic-pituitary axis, it would be important to document this by a cause-and-effect relationship. In other words, it should be possible to induce ovulatory

Table I. The effect of DHA withdrawal upon restoration of serum gonadotropins

Group	*Ovarian weight (mg./100 Gm. of body weight)*	*Uterine weight (mg./100 Gm. of body weight)*	*FSH (ng./ml.)*	*LH (ng./ml.)*
1. DHA* (27-47)	28.5 ± 3	153.0 ± 2	33.0 ± 4	< 10
2. DHA (27-47) (killed on Day 50†)	15.4 ± 1	108.0 ± 4	39.0 ± 6	13.0 ± 7
3. DHA (killed on Day 54‡)	27.2 ± 4	157.3 ± 9	134.0 ± 64§	159.0 ± 91§

*Rats were treated with DHA for 20 consecutive days, and treatment was terminated at 47 days of age, at which time they were killed.

†Same protocol as in Group 1; however, rats were killed at 50 days of age. Note increase in serum LH.

‡Same protocol as in Group 1, but rats were killed seven days later, at 54 days of age. Note increase in serum LH and FSH.

§Denotes significantly different from Group 1 ($p < 0.05$).

Table II. Incidence of presumably ovulatory cycles following clomiphene. Dosages varied from 50 to 200 mg. for 5 days. Occasionally up to 100 mg. was given for 10 days (modified from Greenblatt and associates[57]).

Condition	*No. of patients*	*No. of cycles*	*Ovulation*	*Percentage*
Oligomenorrhea	87	418	343	82.0
Secondary amenorrhea	75	465	297	63.9
Primary amenorrhea	18	109	26	23.8
Stein-Leventhal syndrome	42	165	149	90.0
Dysfunctional uterine bleeding	35	174	147	84.5
Total	257	1,331	962	72.7

failure and polycystic changes in the ovary by androgen administration and the reversal of these events by androgen withdrawal. For such a demonstration, one must turn to experimental models as this type of work can not be done in the human subject. An appropriate model would be useful in providing a system for exploring the mechanisms of the ovarian changes and ovulatory failure and thus provide a working hypothesis for the human syndrome. In the past, the neonatally androgen-sterilized rat has been suggested as a model, but this is unsuitable because of the absence of continued androgen insult as well as the absence of reversibility to cyclic ovulatory function. In 1969, Black and Mahesh[52] reported that the administration of dehydroepiandrosterone to immature rats resulted in a single precocious ovulation followed by ovulatory failure and the formation of cystic ovaries (Fig. 14). The ovulatory failure persisted throughout the period of androgen administration. Studies of serum gonadotropins during the precocious ovulation and subsequent androgen administration were carried out in our laboratory by Knudsen and colleagues.[53] Fig. 15 shows the ovulatory surge of both FSH and LH on Day 30. This was followed by base-line levels of FSH and very low levels of LH throughout androgen administration. An increase in serum LH was seen within three days of the withdrawal of androgen treatment, and statistically significant elevation of both FSH and LH occurred within seven days (Table I). Thereafter, normal cyclicity and fertility occurred. Caution must be exercised in extrapolating the results of these animal studies to the human subject because of species differences.

Management

Allusion was already made to psychogenic factors and also to the fact that corticosteroids may be employed to induce ovulation. When an analogue of chlorotrianisene,* known as MER-25, was made available for clinical trial, Tyler and co-workers[54] reported, in 1960, that this antiestrogen successfully induced ovulation, an observation later confirmed by Kistner and Smith[55] in four cases of Stein-Leventhal syndrome. This drug was removed from clinical investigation because of toxic reactions. About this time, another analogue, MRL-41, also an antiestrogen, was made available for clinical trial as a possible oral contraceptive. It failed as such but proved eminently satisfactory as an ovulation-inducing agent. In 1961, Greenblatt and his colleagues[56] reported that 28 of 36 amenor-

*Tace, Wm. S. Merrell Co., Div. Richardson-Merrell, Inc., 110 E. Amity Rd., Cincinnati, Ohio 45215.

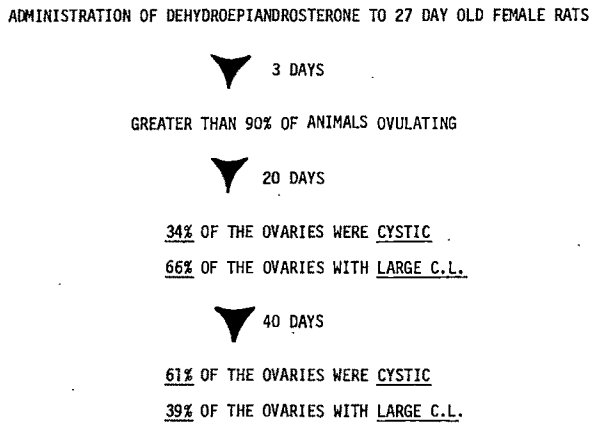


Fig. 14. The effect of dehydroepiandrosterone in causing polycystic changes in the ovary. (From Greenblatt, R. B., and Mahesh, V. B.: J. Reprod. Med. **13:** 87, 1974.)

rheic women ovulated following a course of this agent, later to be known as clomiphene. Clomiphene was employed in a variety of anovulatory conditions, and the best results were obtained in the treatment of the Stein-Leventhal syndrome[57] (Table II). Even women who responded with ovulatory menses to wedge resection for but a few months frequently ovulated after administration of clomiphene. When clomiphene alone does not seem to work, a few days later, an intramuscular injection of 5,000 to 10,000 U. of HCG may be administered.[58] Clomiphene-resistant patients frequently respond to such a regimen.

As a last resort, one may use human pituitary gonadotropins as propounded by Gemsell and coworkers[59] or the more readily available human menopausal gonadotropin,* as employed by Lunenfeld and associates[60] (Fig. 16). A warning should be sounded in the treatment of women with the polycystic ovary syndrome with either clomiphene or gonadotropins. The ovaries of such patients are quite sensitive, and minimal dosages should be used to avoid an hyperstimulation syndrome.

The ideal ovulation-stimulating agent in this disorder, it was hoped, would be LRF. Unfortunately, FSH response is poor though the LH response appears good, and only an occasional patient ovulated following its use. However, LRF followed by HCG or clomiphene followed by LRF has yielded some encouraging results.

Summation

Some assumptions may be drawn from the evidence at hand as to the pathogenesis of the polycystic ovary.

*Pergonal, Cutter Laboratories, Inc., 4th & Parker Sts., Berkeley, California 94710.

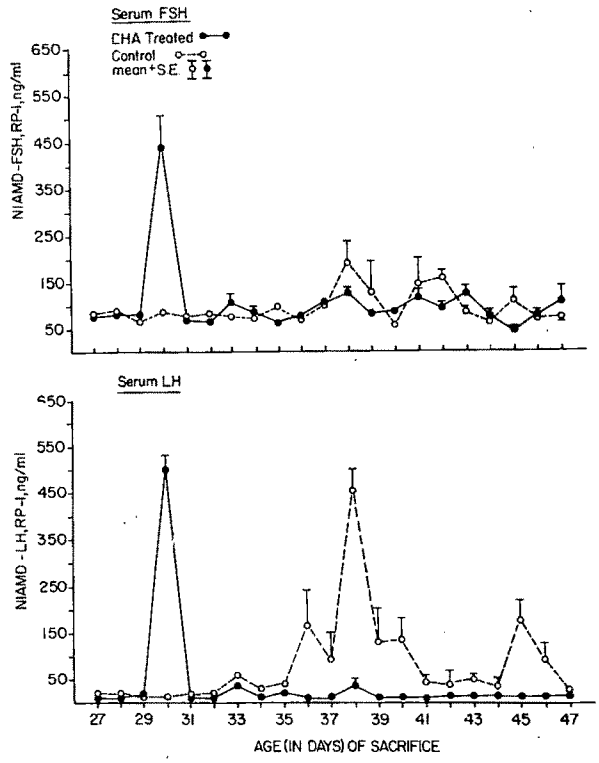


Fig. 15. Effect of DHA administration on serum gonadotropins in the immature female rat (solid lines). After a precocious surge of FSH and LH on Day 30, resulting in ovulation, FSH levels returned to normal base-line levels whereas LH levels were very low. The dotted lines show the gonadotropin changes in untreated rats through the first ovulation on Day 38 and the second on Day 45.

We believe it is fair to say that the higher centers of the brain are influenced by elevated circulating androgens, leading to a discordance in the hypothalamic-pituitary-ovarian axis. The very fact that under certain stress situations ovulation can take place is proof enough that the disturbance in the axis is functional and not organic.

Lloyd[61] provided evidence that hirsute women are more responsive to a test dose of ACTH than normal women by secreting larger amounts of urinary 17-ketosteroids. This feature may well be genetic since we have had several sisters with polycystic ovaries and marked hirsutism. Study of blood obtained by catheterization of the ovarian and adrenal veins revealed markedly elevated levels of androgens and particularly testosterone in women with polycystic ovaries in comparison with normal control subjects. Adrenal values, as a rule, were higher than ovarian levels. It could be assumed because of an inherent capacity of the adrenals, and perhaps the ovaries too, to produce excess androgens, that a train of reactions is

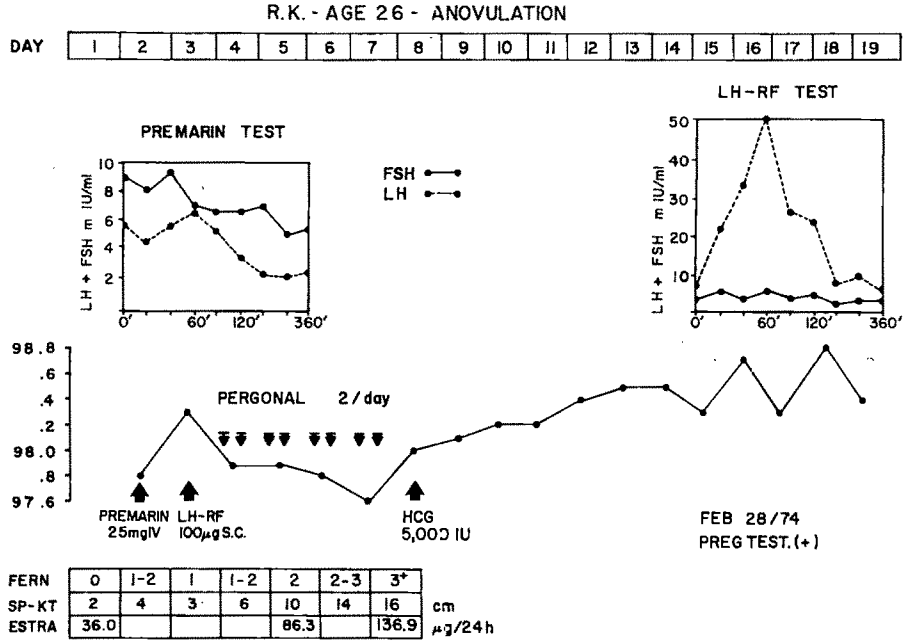


Fig. 16. Pergonal induction of ovulation resulting in conception. Note that prior to Pergonal therapy a lowering of FSH and LH levels was obtained following 25 mg. of intravenous Premarin (Ayerst Labs., Div. American Home Products Corp., 685 Third Ave., New York, New York 10017) and marked LH rise following 100 mcg. of LRF subcutaneously. Also note monitoring of Pergonal administration by fern formation and spinnbarkeit of cervical mucus and urinary estrogen levels.

initiated which ultimately leads to the development of polycystic ovaries.

An explanation for the finding that the majority of women with polycystic ovaries have low serum FSH and normal or slightly elevated LH may be found in the experiment in which testosterone was administered to women. The FSH levels were mildly suppressed while LH remained unchanged or rose slightly.[62] This is reminiscent of the pituitary-testicular axis where LH levels remain more or less constant with little flux.

It appears then that an inherent capacity for androgen production by the adrenal upsets hypothalamic-pituitary-ovarian relationships. As a result, a steady state of discordant gonadotropin secretion stimulates the growth of a myriad of follicles, luteinizing the theca and often certain cellular elements in the stroma. As a consequence, the ovary usually enlarges and elongates; absence of ovulations is reflected in the smooth, glistening capsule. Priming the pituitary pump causes a derangement in orderly ovarian steriodogenesis, resulting in increased androgen production. Thus, the bourgeoning polycystic or microcystic ovary becomes an "androgenic ovary."

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ITEMS

What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.

Registry of Clear-Cell Adenocarcinoma of the Genital Tract and Other Cancers That May Arise in Diethylstilbestrol-Exposed Patients

Effective July 1, 1976, the administrative, epidemiologic, and clinical activities of the Registry will be transferred to Chicago with Arthur L. Herbst, M.D., Director. The new address is: MARP, 303, 5841 S. Maryland Ave., Chicago, Illinois 60637. Telephone: (312) 947-5350. Pathology study will continue with Dr. Robert E. Scully and colleagues at the Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts 02114.

The Registry is investigating: 1. all cases of clear-cell adenocarcinoma of the genital tract occurring in female subjects born after 1940, *whether or not* there is a history of maternal medication; (2) all genital tract cancers including invasive squamous cell carcinomas that may occur in the diethylstilbestrol-exposed population.

Satellite Symposium—Vth International Congress of Endocrinology on Hormone Control in Fetal Development

We have the pleasure in announcing that a Satellite Symposium to the Vth International Congress of Endocrinology on Hormone Control in Fetal Development will be held in Paris on July 26, 27, and 28, 1976. The scientific program includes lectures by invited speakers on the following topics:

1. Cell recognition factors
2. Fetal-maternal-placental relationships
   a. Immunology
   b. Placental hormone—state of the art
3. Fetal tissues
   a. Growth and differentiation
   b. Programming
   c. Hormone binding
   d. Mechanism of action
   e. Biosynthesis and metabolism
4. Sex differentiation
5. Fetal neuroendocrinology

All the papers and discussions presented in the different sections will be published in a special issue of the *Journal of Steroid Biochemistry* five to six months later and in a special book. The full text of the lectures should be ready by July 15, 1976. The official language will be English. The Symposium will be held at the Hotel Sofitel Paris, 2 Rue Grognet, 75738 Paris, Cedex 15. Telephone: 657-1143. The registration fee is $75 (350 French francs) which will include one copy of the Proceedings of the Symposium, three lunches, and a reception, as well as other social arrangements. For further information, write to: Dr. J. R. Pasqualini, Foundation for Hormone Research, 26 Boulevard Brune, 75014 Paris, France. Telephone: 539-9109.

22nd Annual Meeting of the Southern OB-GYN Seminar

The Southern OB-GYN Society will hold its annual meeting in Asheville, North Carolina, on July 18-23, 1976, at the Great Smokies Hilton. The program will cover a broad aspect of obstetrics and gynecology and among program participants will be the Departments of Obstetrics and Gynecology at Duke University, the University of North Carolina, Bowman Gray School of Medicine, and the Medical College of Virginia.

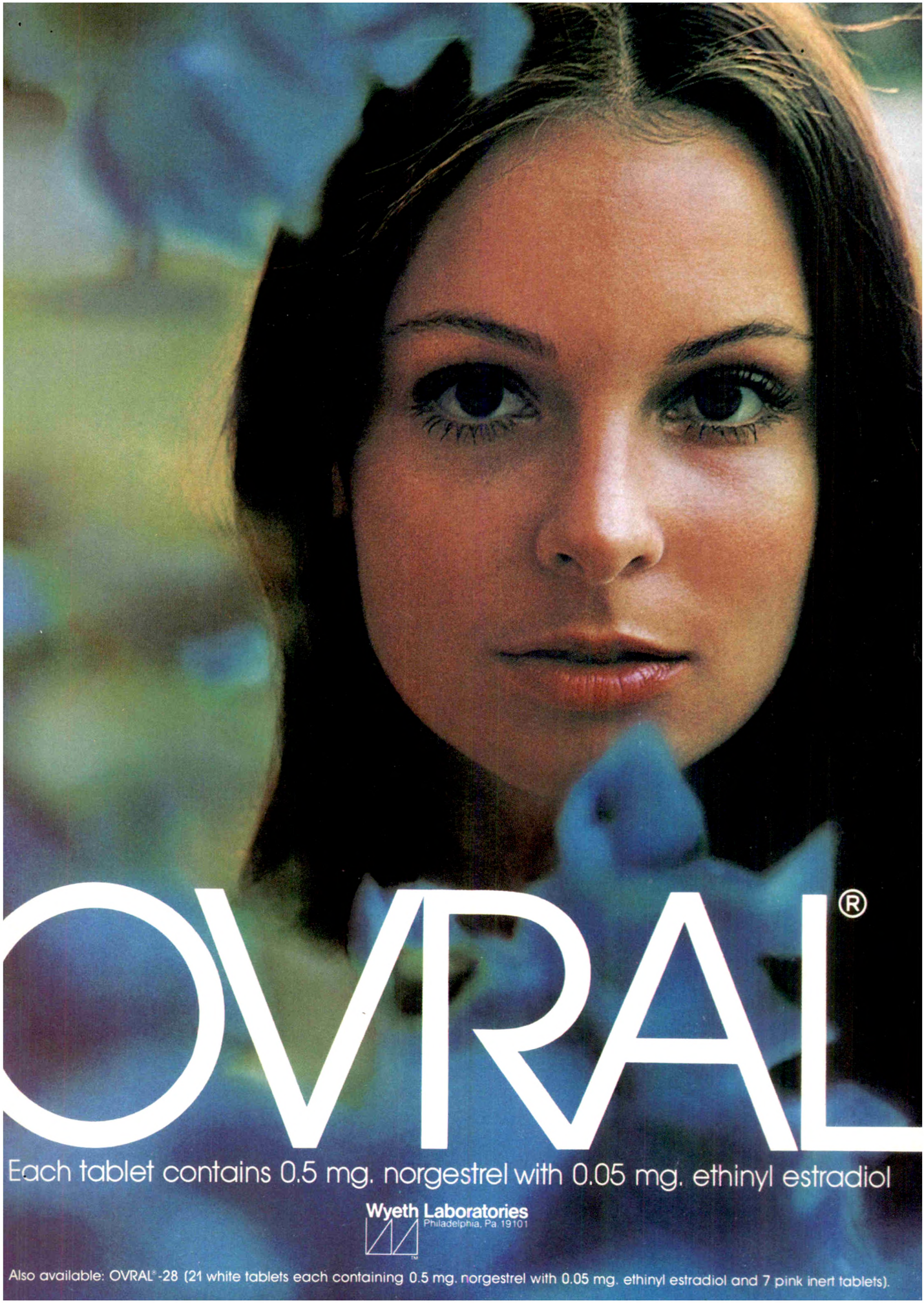
For further information as to registration, please contact the secretary: Dr. George T. Schneider, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121.

Review Course in Obstetrics and Gynecology

Columbia University College of Physicians & Surgeons announces its annual postgraduate course entitled, "Review Course in Obstetrics and Gynecology," to be held at Columbia-Presbyterian Medical Center, Monday through Friday, October 25-29, 1976. Some of the speakers are Drs. R. Vande Wiele, R. Richart, R. Neuwirth, associates, and guest lecturers. It will include a survey of the major clinical and pathologic problems pertaining to the female reproductive system. Emphasis will be on the diagnosis and management of obstetric and gynecologic disorders, including infertility, endocrine problems, and malignant diseases, with the use of modern advances in basic knowledge and clinical practice. There will be a review of gynecologic pathology. The course is divided as follows: gynecologic oncology, perinatal medicine, gynecology and obstetrics, reproduction control behavior, and endocrine disorders. The fee is $250 (residents $125). For registration, write to: Jose M. Ferrer, Jr., M.D., Associate Dean, 630 W. 168th St., New York, New York 10032. Telephone: (212) 694-3682.

International Symposium on Hypertensive Disorders in Pregnancy

There will be an International Symposiom on Hypertensive Disorders in Pregnancy in Muenster, Westf., Federal Republic of Germany, August 24 to 26, 1976. The following topics will be discussed: morphology of the kidney, pathophysiology, endocrine aspects, placenta and uterine blood flow, treatment aspects, and nomenclature. Free communications will be presented only in a limited number. Languages include English and German. For information, write to the Congress Secretary: Heinz D. Böttcher, M.D., Universitäts-Frauenklinik, Westring 11, 4400 Münster/Westf., Federal Republic of Germany.


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DATE: October 6-8, 1976.
FEE: $225, includes lunch each day and Syllabus.

PLACE: Vacation Village, Mission Beach, San Diego, California.

This course is acceptable for up to 18 hours of credit toward the CMA and AMA certification program under Category I.

CONTACT: David Allan, M.D.
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- Active in the presence of blood, pus, or vaginal secretions.
- Virtually nonirritating to vaginal mucosa.
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For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

Recommended regimen

In the office, swab the cervix and vulvovaginal area with BETADINE Solution.

Prescribe BETADINE Vaginal Gel (povidone-iodine) as follows: Insert one (1) applicatorful each night, followed the next morning by BETADINE Douche in its therapeutic concentration (2 tablespoonfuls to a quart of lukewarm water).

This regimen is to be followed through the entire menstrual cycle, including the days of menses. If further therapy is warranted, the regimen should be continued through the next two cycles. The patient may be instructed to return for an office visit following two weeks of therapy.

Precaution

If irritation, redness or swelling develop, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

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"The cooperation of patients on a once-daily dosage of iron was significantly better than those taking a thrice-daily preparation."[2]

1. Bonnar, J., et al., Lancet, 1:457, 1969.
2. Porter, A. M. W., Brit. Med. J., 1:218, 1969.

Please see opposite page for Brief Summary.

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Gardner, H.L. and Kaufman, R.H.:
Benign Diseases of the Vulva and Vagina, St. Louis,
The C.V. Mosby Company, 1969, p. 191.

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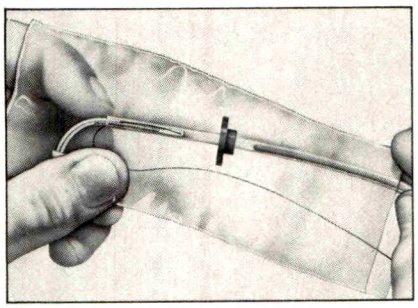
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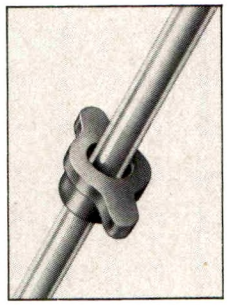


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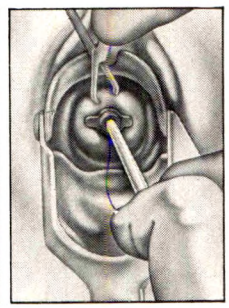
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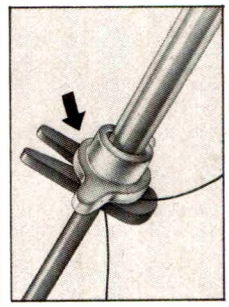
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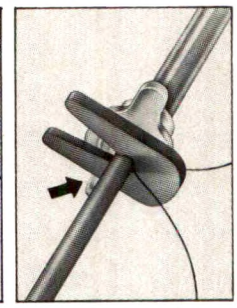
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4. New welded tube-stop
Serves as handle for withdrawing the tube and removal of instrument.



5. New thread-retaining clip
When held to tube-stop during procedure, facilitates insertion and makes tube-crimping virtually impossible.

Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is 89 mg. of pure, virgin electrolytic copper wire providing 200mm^2 of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the copper coil into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication: The Cu-7 is indicated for contraception.

Contraindications: The presence of any of the following, at the time of insertion, constitutes a contraindication: pregnancy, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months, endometrial disease such as hyperplasia or carcinoma and a known or suspected allergy to copper.

Warnings: Recent reports suggest an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. In some cases, initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned of the suggested incidence of increased risk of sepsis and followed with close vigilance.

The long-term effects on the offspring of the presence of copper in the uterus during pregnancy are unknown.

Perforations of the uterus have occurred. In this case the device should be removed immediately.

The use of microwave therapy in patients with metal prosthetics may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients wearing a Cu-7.

Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease, the incidence of which is one in two hundred thousand.

Precautions: A pelvic examination should be done.

Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed shortly following a menstrual period. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed.

Occasional perforations of the uterus (.03%) have been reported, usually during insertion into patients less than two months post abortion or post partum. If penetration into abdominal cavity occurs, laparotomy should be performed and the device recovered. Local inflammatory reaction with abscess formation is a possibility if a device is left in the abdomen.

If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

The Cu-7 should be removed if pelvic infection which is unresponsive to treatment occurs.

The device should be replaced every two years. There is no evidence of decreasing effectiveness with time before two years, but the contraceptive effectiveness of the Cu-7 after two years has yet to be established.

If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to pull on the thread and displace the Cu-7 and told to return in two years for its replacement.

A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman wearing a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being worn.

Adverse Reactions: Perforation of the uterus has occurred.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women.

Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Transient spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. The following complaints have also been reported, although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, and cystitis.

Dosage and Administration: A single Cu-7 is to be inserted into the uterine cavity (see Precautions section). The small diameter of the Cu-7 enables easy insertion into the nulliparous as well as the multiparous uterus. Present information indicates that the efficacy is retained for at least 24 months. Until accurate data indicating a longer effective life become available, the Cu-7 should be removed and a new one inserted on or before 24 months from the date of insertion. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

How Supplied: Available in cartons of 6 and boxes of 30 sterile units (Cu-7 with an inserter) and sufficient patient identification cards.

Clinical Studies: Different event rates have been recorded with the use of different intrauterine contraceptive devices, inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use.) This experience encompasses 321,699 woman-months of use, including 12 months for 9,594 women and 24 months for 7,599.

	12 Months		24 Months	
	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.7	1.3	2.5	2.1
Expulsion	5.5	7.7	6.5	8.7
Medical Removal	9.6	12.7	15.3	18.2
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Please see complete product labeling for insertion and removal techniques.

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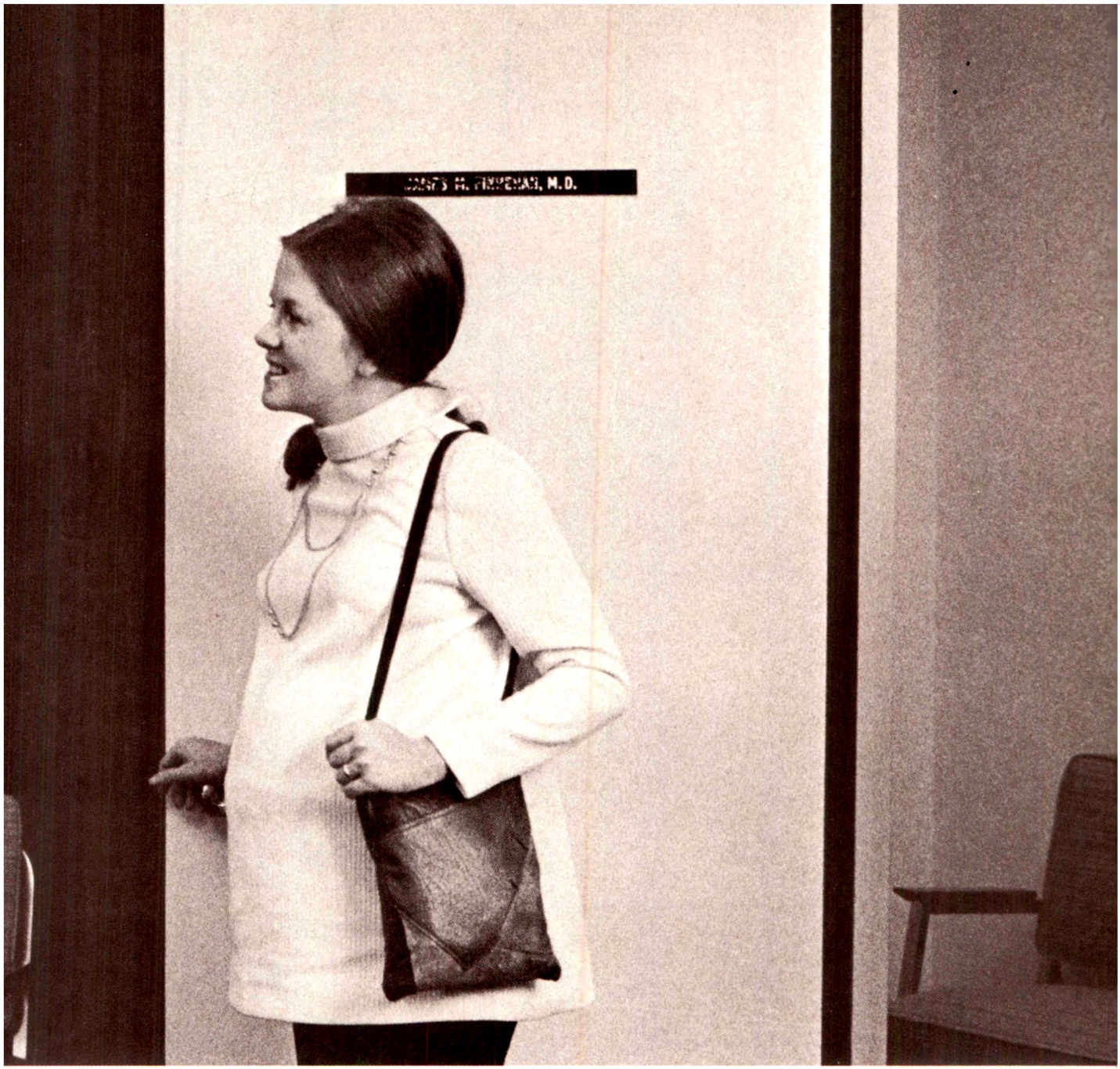
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*Federal Register, 38:20717, Aug. 2, 1973.



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Plus 800 mcg. of Folic Acid

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NOTE: When the offending organism is known, treatment with a specific agent known to be active against that microorganism is preferred.

"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

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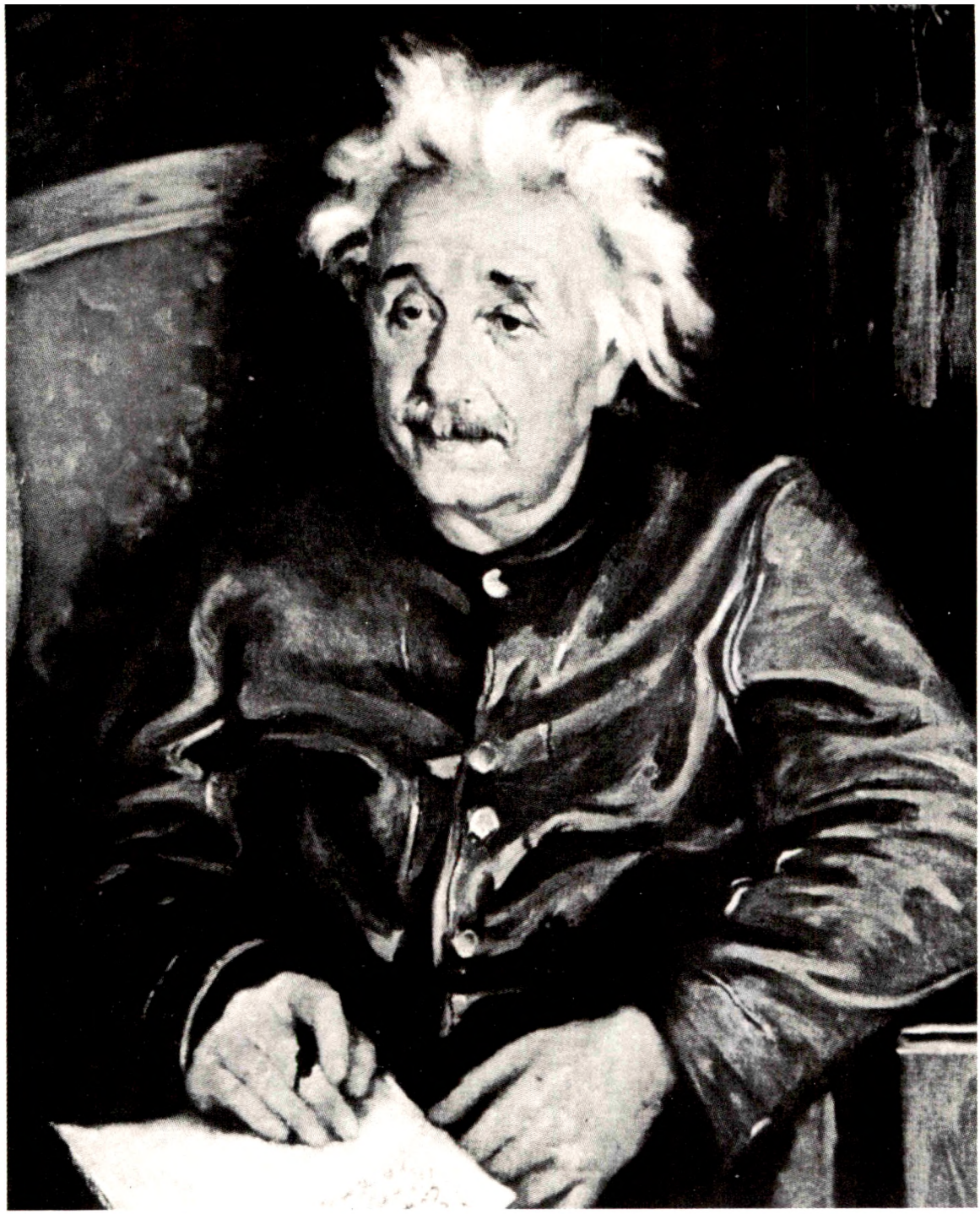
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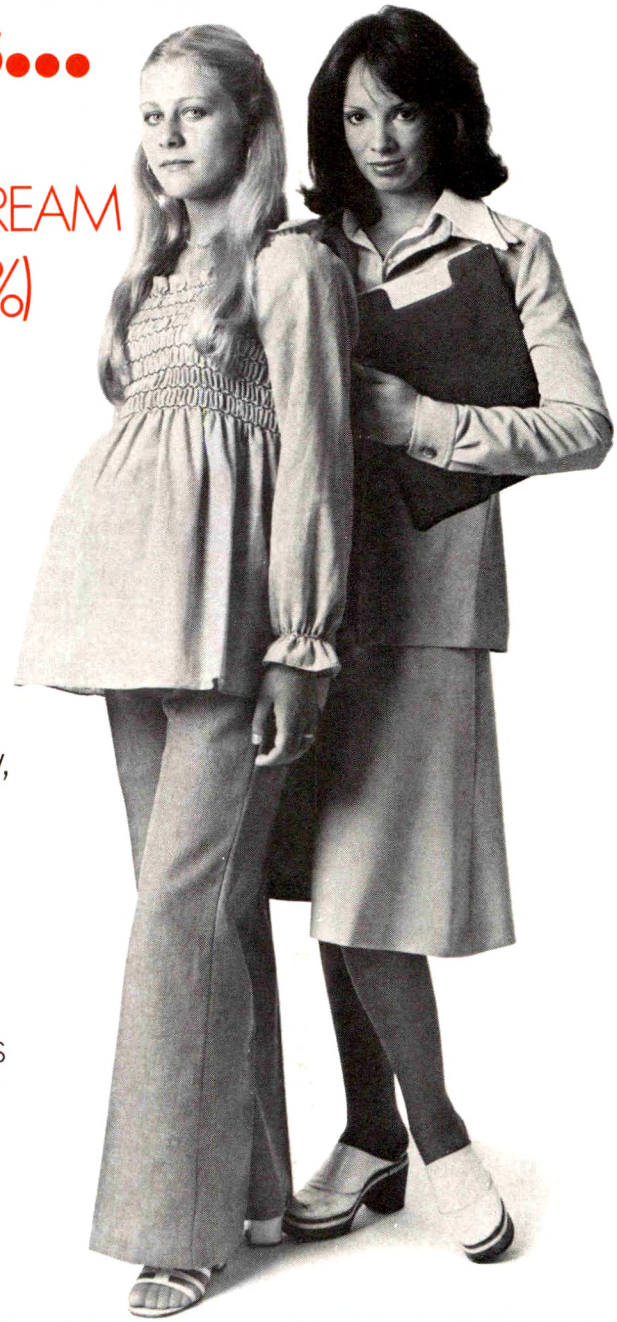
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MONISTAT (Miconazole Nitrate 2%) is a development of Ortho Pharmaceutical Corporation and Janssen Pharmaceutica, Belgium.

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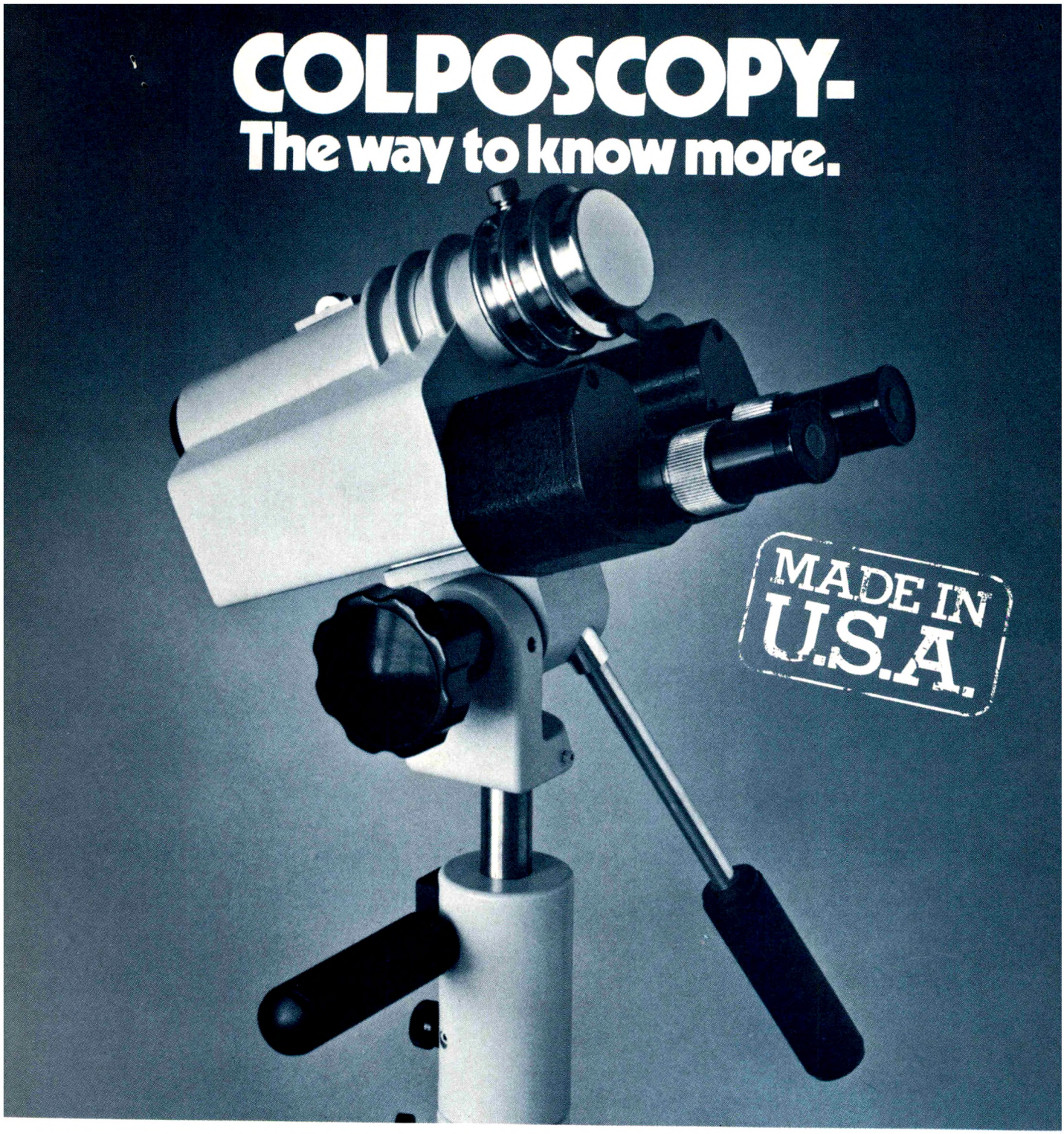
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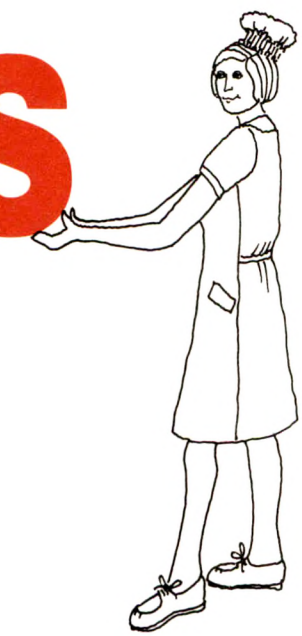
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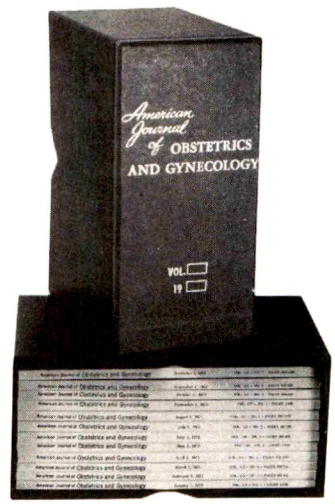
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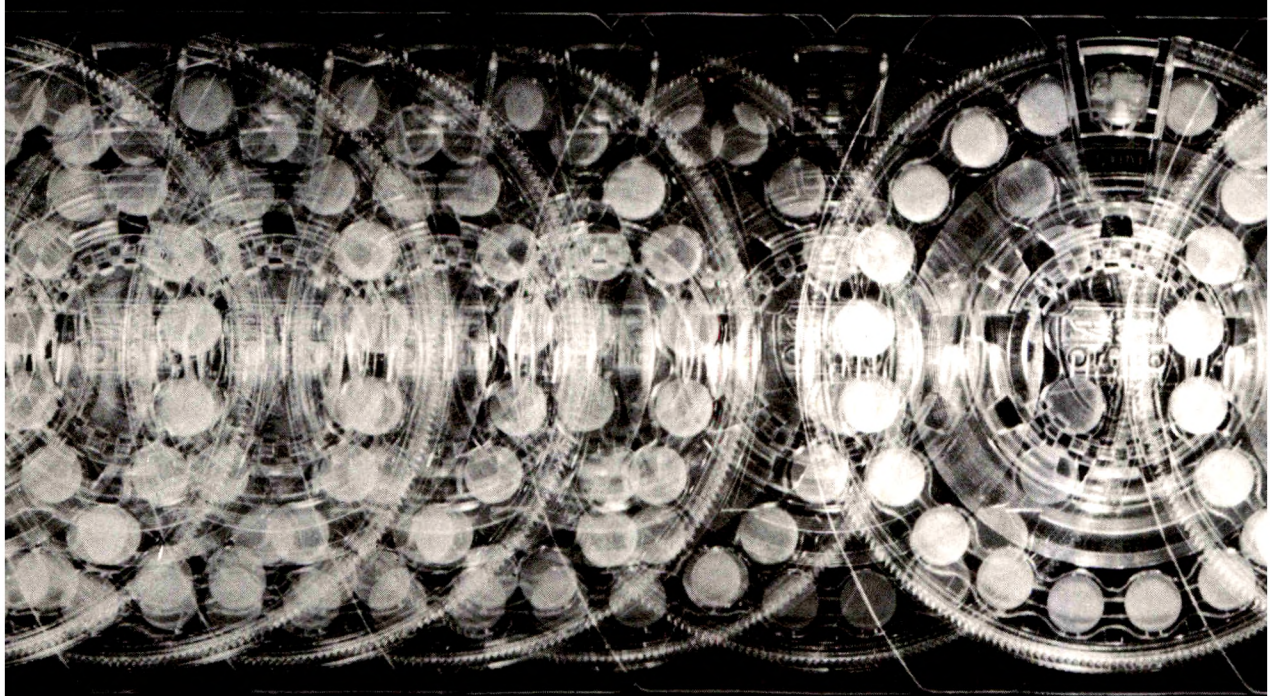
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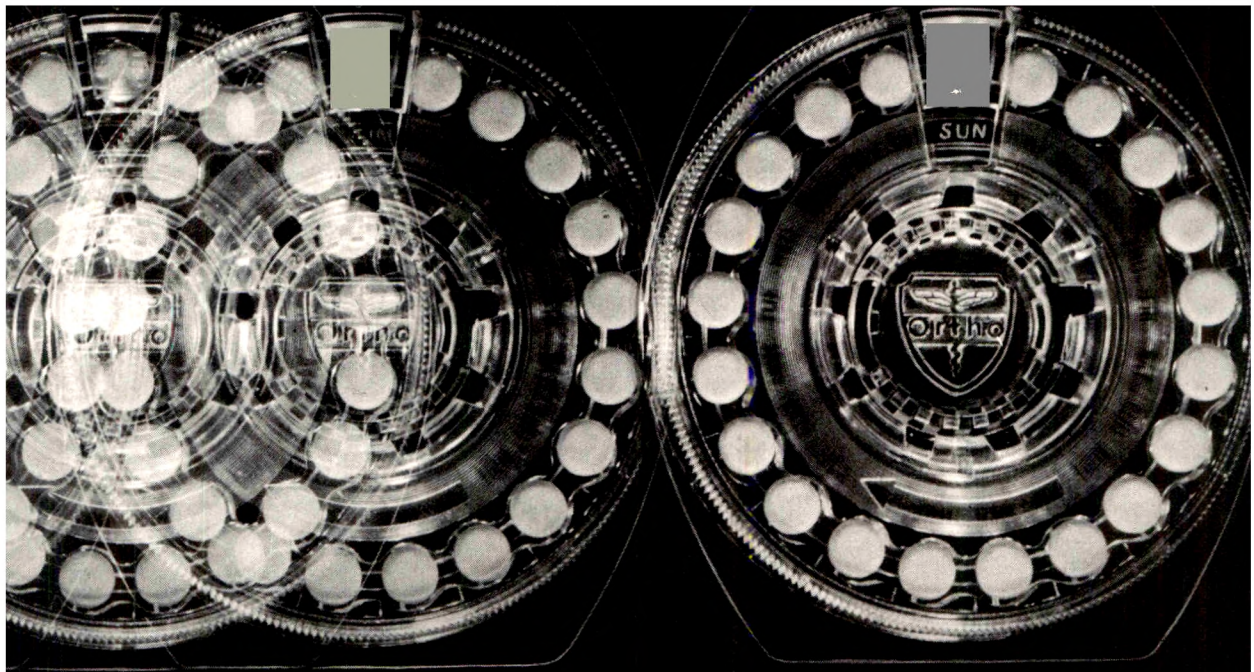
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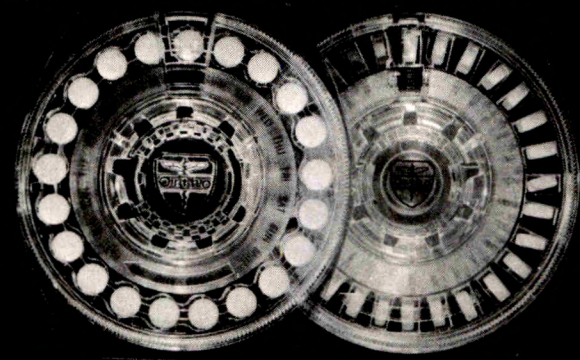
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‡Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

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The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of MODICON in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with MODICON. Therefore, if such tests are abnormal in a patient taking MODICON, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged MODICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving MODICON therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with MODICON may mask the onset of the climacteric. 10. The pathologist should be advised of MODICON therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steriods. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, MODICON should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during MODICON therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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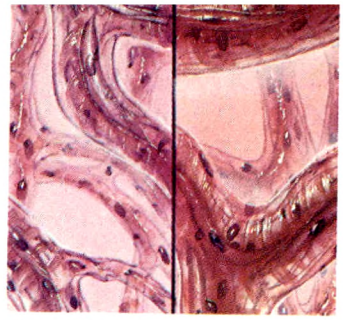
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The menopausal "flush" is believed to result from an autonomic nervous system imbalance due to estrogen deficiency. Here, illustration shows artist's interpretation of "normal" vs. dilated arteriole-capillary-venule network.

"It seemed like I was having one flush after another. It wasn't just a nuisance... it was a real problem."

The menopausal flush is the classic sign of estrogen deficiency...generally recognized as a clear indication for treatment.

This wasn't always the case.

There was a time when the symptoms of the menopause went untreated...when women were expected to suffer the severe flushes and sweats of estrogen deficiency in silence or, at best, with a minimum of encouragement and understanding.

Now, with effective estrogen replacement therapy, women do not have to endure these distressing symptoms. In the great majority of cases, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) can promptly control such vasomotor symptomatology...provide classic relief for classic symptoms during a troublesome period of physiologic adjustment.

Three studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. For further information see "Warnings" in prescribing information.

"The flushes were bad enough... but the sweats at night were almost too much."



For the classic symptoms of the menopause

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



CONTAINS NATURAL ESTROGENS EXCLUSIVELY

See next page for revised prescribing information.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN® Brand of
CONJUGATED ESTROGENS TABLETS, U.S.P.

Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration; however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al.*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)
No. 865—Each *purple* tablet contains 2.5 mg, in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg, in bottles of 100 and 1,000.

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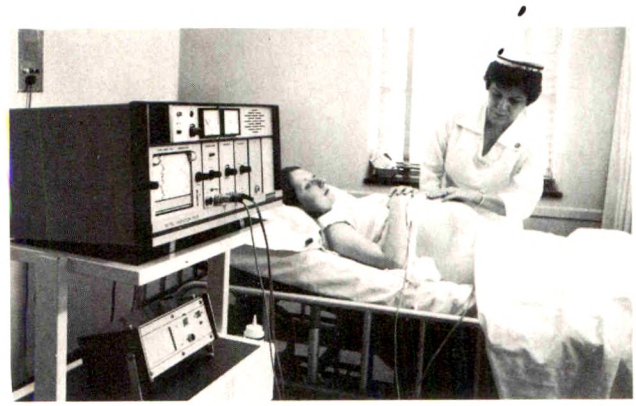
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Ongoing clinical experience confirms a low incidence of breakthrough bleeding† with LO/OVRAL.

In "fresh" patients* and patients switched from other oral contraceptives.

Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials

Cycle	1	12	24	36	Total Cycles 20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment. *These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

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IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness; fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

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American Journal of Obstetrics and Gynecology

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Transactions of the Forty-second Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society

Requiem for private practice

Presidential address

RALPH H. WALKER, M.D.

North Hollywood, California

THE FOLLOWING thoughts are from the viewpoint of a physician who has been in the clinical practice of obstetrics and gynecology for a number of years. Medical practice and educational concepts have changed during those years, and even greater changes are foreseen for the next decade. In this regard, it would be of interest for authors to review papers submitted a few years (or even months) ago to evaluate the material in light of today's thinking. I am well aware that by the time this material is published, changes in procedures and new developments may have occurred to modify the opinions expressed by its author.

What are the current trends relating to the practice of medicine and, more particularly, the practice of obstetrics and gynecology? How many of our recent graduates are going into group practice, how many have chosen to go into academic medicine, how many have selected private practice, and, of the latter group, how many have selected urban areas rather than rural? I ask this question since there has not been one new Ob-Gyn member from a recent graduate program in over 20 years on the staff of the private urban hospital where I practice and where the facilities, personnel, and medical staff are excellent.

Of 100 replies to a questionnaire sent to Ob-Gyn residents who had completed their training in the past 10 years, 69 were in private practice (or in a partnership of their own specialty), 13 were in group practice, 12 were in academic medicine, and six had chosen the military, public health, etc.

Of the 69 in private practice 59 were Board certified and 10 were Board eligible. Not all questionnaires were completely answered but, of the 69 who selected private practice, 47 listed independence as one of their reasons; of the same group, 40 selected urban practice and eight rural practice as a definite choice.

In reply from Jack Hallatt of Kaiser-Permanente regarding Ob-Gyn graduates, 19 of 64 remained with the group (70 per cent left Kaiser-Permanente for varied reasons, and it is not known how many of these went into private practice).

Of the academic group, eight chairmen and four associate chairmen of Pacific Coast medical schools had provided 10 or more years of graduate training.

To the question of whether or not oncology should be a separate subspecialty of gynecology, the majority of this group favored separation and certification. Most, if fact, regarded separation of the divisions of Ob-Gyn as a fact of life, believing that individual aptitude, personal interests, training, etc., would separate the divisions in our rather broad specialty.

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Although oncology is now a Board-certified division of gynecology, requiring additional training, the specialty of oncology itself is splintered into several divisions—surgery, radiation therapy, etc., and it may well be that all malignancy should be treated in specialized departments or centers limited to research, investigation, and the treatment of cancer.

Another developing trend is that of separation of postgraduates from the medical schools. This has increased, especially in some areas, during the past few years, and I think this is unfortunate. Participation of the attending man with the medical school staff or general hospital is of inestimable benefit to both the undergraduate and the practicing clinician. Rather than the professor-student relationship, it should be physician to physician with the common purpose of an exchange of ideas and information. All standard hospitals, particularly those in rural areas, should organize their staffs to participate with university programs in some manner as an adjunct to their continuing education.

Continuing medical education raises many questions. Through the years, the steady increase in scientific knowledge and positive results of research and investigation have been tremendous. We would all agree that it is the physician's responsibility to remain informed, but it becomes an increasingly difficult task for the average physician, academic or otherwise. To read all of the current literature is virtually impossible. Only one third of the clinicians reported they had authored one or more papers for publication. Those in academic life varied from 10 to 92 papers produced in the past 10 years. How long then is the average graduate current in his knowledge and practice? The granting of a license to a physician to practice for life, even though he may never again read a medical book or journal, is no more practical than to grant life tenure to a teacher or judge, or men in other professions. Continuing medical education and peer group review are forms of monitoring which are both practical and probably acceptable for recertification, and would appear to be of greater value than any type of legislative act or governmental control. In the questionnaire, independence was high on the list of priorities of those who chose private practice over group or prepaid health plans. Few private practitioners wish to be dictated to by federal or state governments, or by anyone else. However, it is a fact that government funds now pay approximately 40 per cent of the costs of private hospitalization and 60 per cent of medical school expense. The man who pays the bill may demand that it be itemized and may reasonably expect to use the product. The future may find the practice of medicine controlled by governmental legislation.

The Government Special Projects Grant in the Health Manpower Act, A.M.A., A.A.M.C., the Coordinating Council on Medical Education, and others are urging a 50 per cent rate of primary physicians. Many prepaid health groups have a higher rate of utilization of primary physicians than are in current preferential undergraduate training for family practice. But who, or what, is a primary physician? It would seem that the large general specialties such as internal medicine, pediatrics, obstetrics-gynecology, etc., are in an excellent position to function in this capacity—to provide medical care, diagnosis, treatment, or referral.

The foreign medical graduate poses another problem to the future of medical practice in this country. In 1972 there were 68,000 foreign medical graduates (exclusive of Canadian) practicing in the United States; of these, 28,000 were Asian in origin and were, as in the case of the Philippine Islands and India, from countries in dire need of medical practitioners.

It is true that medical schools would be required to double their capacity and costs if U. S. graduates were to equal and replace the influx of foreign medical graduates in this country; however, since these foreign medical graduates are trained largely in nonaffluent countries, one would expect that we, in the United States, could train our own eligible applicants for medical schools. In 1972-73, for instance, 36,000 applied and 62 per cent of these applicants were turned away. While it is a reality that many foreign medical graduates have contributed substantially to medical care in this country, our first obligation should be to our own eligible applicants to United States medical schools.

At the present time, the Medical Manpower Bill, HR-5541, is proposing to subsidize medical students with the expectation of repayment of the forced subsidy "loan" following graduate education; or the government will excuse repayment if the American medical graduate goes into military service, welfare, or other areas in need of patient care.

In 1972 foreign medical graduates constituted approximately 20 per cent of our medical manpower. The undergraduate training they receive is not as uniform as that of the American medical graduate. Their undergraduate training is not subject to American legislative acts. They are under no restriction as to specialty or location of practice (nor have the American medical graduates been in the past). The foreign medical graduate has not, as a rule, been trained for primary care or family practice. It does not seem logical

Table I. Population and birth rates: L. A. County and state of California

	1964	*1974*
Population, L. A. County (estimated)*	6,743,000	7,100,000
Deliveries (L. A. County)	129,825	103,054
	1965	*1972*
Population (estimated),* state of California	15,885,000	20,411,000
	1964	*1973*
Deliveries: state of California	374,587	297,834

Table II. Obstetrics departments, private hospitals in L. A. County*

	1964	*1974*
Deliveries:		
2,000 births per year	10	3†
1,500-2,000 births per year	11	5
500 births per year	38	34
Totals	59	42

*Discontinued obstetrics department since 1964—29 hospitals.

†Cedars of Lebanon, 4,041 (1974).

Table III. Trend of obstetric practice: Los Angeles County, California

	1964		*1974*	
	No.	*%*	*No.*	*%*
Total private deliveries	99,056		74,531	
LAC/USC Medical Center John Wesley Hospital UCLA Medical Center Harbor General Hospital	23,008	17.7	16,318	15.2
Kaiser-Permanente Health Plan *Ross-Loos (664 in 1964, 840 in 1974)	7,761	6.0	12,205	11.8
Totals	129,825		103,054	
St. Anne Hospital—1974	588			1.6
Santa Marta Hospital—1974	1,015 1,603			
Total percentage				28.83

*No attempt made to include all small prepaid health groups, all charity, home deliveries, etc.

to have a manpower bill that regulates our undergraduate American medical students, but has no similar regulation for foreign medical graduates. Specialization is primarily for the perfection of patient care in a limited field of medicine or surgery, e.g., the subspecialty of gyn-oncology. This will become more of a necessity as we increase our scientific knowledge through sophisticated medical research.

Also, it would seem that the distribution of specialists according to geographic need and patient requirement should be regulated in some way, perhaps through medical school regulation of graduate training, to achieve a better balance of specialty care. According to M.D.'s per 100,000 population, we do not have a serious physician shortage as much as we have specialists not in accord with patient need and, possibly, maldistribution of patient care. The more affluent states and the urban areas have a higher physician to patient ratio.

Finally, it may be stated that there is a great contrast between the perfection of specialty care, continuing medical education, recertification, accreditation, etc. vs. the promotion of health care probided by paramedical personnel, amateur physicians, and others for the purpose of freeing the M.D. for "more important physican responsibilities."

Additional trends in the practice of obstetrics are demonstrated in Tables I, II, and III. The data have been compiled from available statistics for the County of Los Angeles. Los Angeles was selected for this purpose since it would appear that the population is sufficiently large to be used as a cross-section or national trend. Live births recorded in Los Angeles County are approximately one third of the total number of live infants born in California.

Despite the rise in population figures in both the county and state in the 10 year period—1964-74—the figures show a decrease in total birth rate over this same period of time (Table I). There are many reasons for this trend, one of which is the incidence of abortion which at the present time is approaching one abortion to every two live births.

If the accepted minimum to qualify as a standard obstetric department is 2,000 births per year, only three private hospitals in the entire County of Los Angeles qualified during the year 1974, and one of these was Cedars of Lebanon with 4,041 deliveries. In 1964, 10 private hospitals had 2,000 or more births per year. In the 10 year period from 1964 to 1974, a total of 29 private hospitals in Los Angeles County discontinued their obstetric departments. The marked change no doubt has been in the increased care provided by the large prepaid health groups (Kaiser-

Permanente, Ross-Loos, etc.). Modern facilities, perinatology, high-risk mothers, anesthesiologists, intensive care for problem neonates, fetal heart monitoring, etc., comprise ideal care, but no obstetric department can provide this sophisticated type of care without an adequate number of births per year (Table II).

The trend of obstetric practice in Los Angeles County for the 10 year period 1964-1974 is depicted in Table III. These data show the upward trend of deliveries in prepaid health plans and the decrease in the number of private deliveries and those of county and state facilities.

The private practice of medicine is in greater jeopardy than ever before. Admittedly we might have had better general management, more favorable press, etc., but the fact remains that private practice cannot compete financially with prepaid health groups, multiple specialty clinics, HMO's, et cetera. Most private physicians adopt a team approach, calling in other specialists for consultation and assistance as necessary. This insures the physician his choice of consultant and hospital, but accrues added multiple office "overhead" expense to the patient. The future may find us competing for decreasing numbers of patients who prefer private care and can afford its cost.

From the vantage point of having been in active clinical practice for a number of years, I have attempted to delineate a few of the problems of obstetric and gynecologic practice today, and to project those I feel will need solution in the near future.

The Pacific Coast Society is one of the most influential in the United States, with nearly every Pacific Coast medical school represented. Many of our members have been, or are at present, in charge of local, state, and national societies, or advisory councils. For this reason, I have felt free to present this type of paper to this distinguished Society. The Pacific Coast Obstetrical and Gynecological Society is, and should be, influential in establishing medical policy during these important next few years.

Patterns of management with breech presentation

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A review of 12 years' experience with term breech delivery at Overlake Memorial Hospital, Bellevue, Washington, was undertaken to ascertain patterns of care as practiced in a suburban community hospital setting. A total of 402 term breech deliveries were managed by 34 family practitioners and 21 obstetricians. X-ray pelvimetry was found to correlate with clinical pelvimetry in two thirds of the cases when used. There were 314 patients delivered vaginally and 88 by cesarean section (an over-all cesarean section rate of 21.9 per cent). There was a striking increase to 43.9 per cent during the last 2 years of the review. This review indicates increasing utilization of consultation with breech presentation, an increasing percentage managed by obstetricians, increasing use of x-ray pelvimetry, decreasing frequency of prolonged labor, a sharp increase in use of cesarean section, and a decline in perinatal morbidity.

RING THE past 15 years, patterns of management ases of breech presentation have been subjected to cal review. Practicing obstetricians and family ctitioners managing such cases have received a dy flow of advice regarding evaluation and delivery heir patients. The advice is largely based on clinical lies conducted in institutions in which some uniity of management is coordinated with a postduate training program. Much study has been cted at antepartum evaluation and has culminated the Zatuchni-Andros[1] prognostic scoring index. h evaluation seeks to identify high-risk patients and been demonstrated to be valid in the hands of ers.[2] The use of x-ray to rule out bony abnormality hyperextension of the fetal head and to evaluate ic capacity has been widely recommended.[3-6] mation of fetal size and, more recently, ultrasonic surement of the fetal head is reported to be useful ntepartum evaluation.[3, 7]

he choice of method of delivery has received ial attention and we have been warned of the gers of total breech extraction.[8, 9] Others use action to avoid hypoxia that might accompany a delivery.[3] Consideration has been given to elective rean section for patients with breech presentation ring labor at or near term.[10] Careful evaluation of r correlated with pelvimetry and fetal size has been utilized to select patients for cesarean section or vaginal delivery after a trial of labor.[4, 6] Oxytocic augmentation of labor has been cautiously recommended.[2, 4, 6, 11]

This review was undertaken to ascertain the patterns of care practiced by family practitioners and obstetricians in a nonteaching community hospital environment. Overlake Memorial Hospital is a 150 bed general hospital located in Bellevue, Washington, a residential community on the eastern shore of Lake Washington, approximately 10 miles from Seattle and the University of Washington Medical School.

Materials

The review includes all term breech deliveries at Overlake Memorial Hospital for a 12 year period from 1963 through 1974. During this period there were 17,551 births and there were 402 cases of breech presentation in which the infant weight was 2,500 grams or greater after exclusion of cases of twins, repeat cesarean sections, perinatal death associated with abruptio placentae, fetal anomalies incompatible with life, severe erythroblastosis, and deaths in utero prior to the onset of labor and not associated with breech presentation. The hospital clinical records and prenatal records of each case were reviewed. One clinical record was missing and the information was extracted from the delivery room register and the attending physician's office records.

Analysis of data

The 402 cases of term breech presentation at risk were rather evenly divided between 191 nulliparous patients and 211 multiparous patients. There were 284

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Table I. Utilization of x-ray pelvimetry

	Total cases	*X-ray pelvimetry obtained*	*Percentage utilized*
1963-74	402	115	29
Nulliparas	191	92	48
Multiparas	211	21	10
1963-68	177	32	18
1969-74	225	83	37

cases of frank breech presentation and 118 cases of footling presentation. Several cases of complete breech presentation are included with the footling presentations. It was not uniformly possible to detect at what stage of pregnancy breech presentation was diagnosed, but records indicated that in 70 cases breech presentation was a surprise finding in labor. There was no accurate record of previously attempted external version but some cases had references to this procedure. There were seven cases in which pre-eclamptic toxemia was diagnosed prior to or at the onset of labor and there were four cases complicated by maternal diabetes mellitus. There were four cases in which obesity was considered a complication. Thirty-four family practitioners managed a total of 130 cases and in 43 cases obtained consultation from an obstetrician. There was a sharp increase in frequency of consultation during the latter years of the review. The remaining 272 cases were managed by 21 obstetricians. During the first half of the review, 53 per cent of cases were managed by obstetricians; during the second half, 79 per cent of cases were managed by obstetricians. In the cases managed by obstetricians, it would appear that consultation was largely a formality prior to cesarean section as 60 of 65 consultations obtained were associated with prompt delivery by cesarean section.

The 402 cases were in all instances evaluated by clinical pelvimetry. The utilization of x-ray pelvimetry is listed in Table I. Seventy-six of the 115 x-ray measurements were found to correlate with the previous clinical estimates but in 39 cases the measurements did not correlate. Of special significance were 26 cases in which the clinical impression of an adequate pelvis was associated with a relatively contracted pelvis by x-ray measurement. These cases were usually found after failure to make adequate progress in labor. There was a clear trend toward increasing utilization of x-ray pelvimetry.

The method of delivery in the 402 cases included 314 vaginal deliveries and 88 cesarean sections for an over-all cesarean section rate of 21.9 per cent. The method of delivery and the anesthesia utilized are listed in Table II.

There were 12 cases of diagnosed prolapsed umbilical cord. Four occurred with frank breech presentation and eight complicated footling presentations. Five of the prolapses occurred at or near complete dilatation of the cervix and were managed by prompt vaginal delivery. The five infants survived with no known morbidity aside from initial low Apgar scores. Six cases occurred earlier in labor and were managed by prompt cesarean section with no morbidity. One case occurred at 6 cm. dilatation with evidence of fetal death shortly after diagnosis. A 3,487 gram stillborn infant was subsequently delivered vaginally.

There were 10 cases in which the duration of labor was in excess of 20 hours. All 10 cases listed in Table III occurred during the first 7 years of the review and none during the last 5 years. Of special interest was a 26 hour labor in which a consultant advised cesarean section. Delivery of a 3,430 gram infant by "difficult" extraction was accomplished. The average weight of the infants in the 10 cases of prolonged labor was 3,295 grams.

There were 16 cases in which the infant weighed in excess of 9 pounds (4,082 grams.) The largest was 11 pounds 9 ounces (5,245 grams.) These cases are listed in Table IV. As noted, there were eight vaginal deliveries, none of which had x-ray evaluation. One infant suffered a fractured clavicle and Erb's palsy. Another, with multiple contusions, made an uneventful recovery. The average duration of labor in the eight vaginal deliveries was 7 hours.

Among the 402 cases reviewed, there were five perinatal deaths. These included the death with prolapsed cord previously noted. There were three cases of death occurring during the second stage or during delivery with no ready explanation. One postmortem examination revealed bilateral adrenal hemorrhage, one postmortem examination revealed no apparent cause of death, and the third infant was not examined. In one case of ruptured bag of water at term in early labor, fetal distress was diagnosed because of irregular and slow fetal heart tones. Cesarean section was accomplished with delivery of a depressed infant. The infant developed respiratory distress syndrome and died. Postmortem examination revealed hyaline membrane disease. The loss of these five term infants represents a probably correctable perinatal mortality rate of 1.24 per cent.

The 402 breech deliveries were associated with 23 recorded cases of perinatal morbidity. These are listed in Table V. The list includes 11 cases of traumatic fetal injury. Six of these were delivered by assisted breech delivery and five by extraction. The perinatal morbidity was spread evenly through the first 8 years of the

Table II. Method of delivery and anesthesia utilized in 402 cases of breech presentation

Type of delivery	*No.*	*Anesthesia utilized*				
		None	*Local*	*Spinal*	*Epidural*	*General*
Precipitous	5	5				
Assisted breech delivery	245		67	22	78	78
Breech extraction	64			11	21	32
Cesarean section	88			59	2	27
Total	402	5	67	92	101	137

Table III. Ten cases of prolonged labor in excess of 20 hours (Average infant weight, 3,295 grams)

	No. of cases
X-ray pelvimetry utilized	1
Syntocinon augmentation	5
Method of delivery:	
Assisted	6
Extracted	2
Cesarean section	2
Morbidity (dislocated hip)	1

Table IV. Sixteen infant weights in excess of 4,082 grams

	Morbidity
Eight delivered by cesarean section	0
6 after failed labor:	
2 had x-ray pelvimetry	
2 prior to labor:	
both had x-ray pelvimetry	
Eight delivered vaginally	2
(no x-ray pelvimetry obtained)	
4 by assisted breech delivery	
4 by extraction	2

Table V. Perinatal morbidity in 402 cases of breech presentation

	No. of cases
Respiratory distress syndrome	8
Atelectasis	2
Pneumothorax	1
Fractured clavicle	4
Fractured clavicle and Erb's palsy	1
Erb's palsy	1
Fractured femur	1
Dislocated hip	1
Contusions, multiple	3
CNS injury	1
Total	23

Table VI. Indication for cesarean section in 402 cases of breech presentation

	No. of cases
Prolapsed umbilical cord	6
Fetal distress	2
Low-lying placenta	1
Failed labor	56
Elective	23
Total	88

Table VII. Fifty-six cesarean sections for failed labor

	No. of cases
Syntocinon augmentation	13
X-ray pelvimetry utilized	38
Normal measurements	17
Less than normal	21
No x-ray pelvimetry	18
Morbidity	3 (RDS)

series. There were no serious traumatic injuries during the last 4 years of the study.

Eighty-eight of the 402 cases were delivered by cesarean section. The recorded indications for cesarean section are listed in Table VI. Twenty-three of the cesarean sections were elective at the onset or prior to the onset of labor. Three of these had ruptured membranes. Fifteen of these 23 had x-ray pelvimetry, of which 10 revealed less than adequate pelvis. The average weight of these infants was 7 pounds 14 ounces (3,570 grams). The largest was 11 pounds 9 ounces (5,245 grams) and the smallest was 5 pounds 9 ounces (2,523 grams).

There were 56 cesarean sections accomplished after a trial of labor with inadequate progress. These are listed on Table VII. The average infant weight in these trial labor cases was 7 pounds 9 ounces (3,442 grams). The only morbidity in these 56 cases was transient respiratory distress syndrome in three cases.

During the first 6 years of the review, the cesarean section rate was 14.7 per cent. During the second 6 years, the rate increased to 27.6 per cent. Especially striking is the comparison between the beginning and the end of the series. During the first 2 years, the rate was 2.5 per cent (one of 40 cases); during the last 2 years, the rate was 43.9 per cent (25 of 57 cases).

Table VIII. Fifty-six cases in which oxytocin was used in labor

	No. of cases
Elective induction in which breech presentation diagnosed in labor	9
Failed labor—delivered by cesarean section (average time in labor, 12 hours)	13
Morbidity	0
X-ray pelvimetry	6
Delivered vaginally (average time in labor, 9 hours)	43
In excess of 20 hours	4
X-ray pelvimetry	7
Morbidity	7

Table IX. Maternal complications of 402 breech deliveries

	No. of cases
Cervical laceration with hemorrhage requiring transfusion	1
Ruptured uterus with hysterectomy	1
Hypotensive episode and respiratory arrest	1
Postpartum hemorrhage with transfusion	1
Blood loss anemia	2
Endometritis	2
Urinary tract infection	2
Urinary retention	1
Superficial thrombophlebitis	1
Cesarean section wound abscess—*E. coli*	1
Episiotomy breakdown	1
Anxiety reaction (morbid infant)	1
Total	15

There were 35 cases in which x-ray pelvimetry indicated less than an adequate pelvis: 26 of these were delivered by cesarean section and nine were delivered vaginally. None of these nine infants was large. The average weight was 3,166 grams (7 pound 0 ounces). One infant suffered a dislocated hip and another multiple contusions with ecchymosis.

There were 56 cases in which oxytocins were used in labor as listed in Table VIII. As noted, x-ray pelvimetry was utilized in 13 cases. The records are not always clear as to whether the x-ray was obtained prior to or during the oxytocin augmentation. The 43 cases delivered vaginally included seven difficult extractions with four infant injuries and three respiratory problems.

There were 15 maternal complications of delivery recorded. These are listed on Table IX.

Comment

Many of the published accounts of breech management refer to their protocol or plan of management and then proceed to compare their perinatal results with other published series.[3, 4, 11] The 402 cases of term breech presentation managed by 55 private staff physicians in a small community hospital offer a considerable contrast. The more sophisticated methods of antepartum evaluation are not routinely applied when a family practitioner or obstetrician has an occasional case of breech presentation to manage. When all appears to be progressing well, both family practitioners and obstetricians appeared to be satisfied with clinical evaluation of the pelvic capacity in most instances. The factors utilized by Zatuchni and Andros[1] in assigning a prognostic score were noted in many prenatal records, admission notes, labor notes, and consultation notes, but the prognostic scoring system per se was not used during the closing years of this review.

The surprise findings of breech presentation during labor is reported in equal numbers by others.[9] The diagnosis of breech presentation in nine cases during the course of elective induction would suggest more careful evaluation of all induction cases to determine presentation.

In a community hospital setting, the choice of anesthesia appears to be largely an individual preference and is somewhat dependent upon availability. Happily, the anesthesiologist can serve as a nonofficial consultant to the family practitioner in such matters. The apparent preference for assisted breech delivery over extraction seems well entrenched. While fetal injury is less common with assisted delivery, it does remain a threat, especially injury to the arm, shoulder-girdle, neck, and head.

The observation and management of labor does not seem to follow a definite pattern, but it would appear that prolonged labor was taken less seriously during the initial years of the review. The failure to utilize x-ray pelvimetry in cases of prolonged labor is difficult to understand. The fortuitous outcome in cases of failed labor subsequently delivered by cesarean section reinforces the observation that the danger to the infant is not in the labor but in the delivery.[6] The use of syntocinon augmentation of labor without x-ray evaluation is seriously questioned.

The striking increase in utilization of cesarean section during the closing years of this review reflects the influence of several factors. The tendency to have each child in a small family assume a premium baby status has been commented on by others.[5] The probable preventibility of all deaths in this series by prompt cesarean section at the onset of labor would fit into a pattern of management suggested by Wright[10] over 15 years ago. It would seem that the family practitioner and obstetrician responsible for an occasional breech delivery is re-evaluating the risk factors and is choosing the most reliable method of introducing an undamaged infant into a small family.

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Discussion

DR. RALPH C. BENSON, Portland, Oregon. I have been most interested in Dr. Wolter's paper, which is both pertinent and provocative. He is to be commended for his broad evaluation of an open-staff, nonteaching, general hospital experience and for introducing this topic again for our thoughtful consideration.

Without resort to version, breech delivery normally occurs in 3 to 4 per cent of term pregnancies, depending mainly upon the incidence of cesarean section at that particular institution. Dr. Wolter's incidence of breech births (≥2,500 grams, some of which may well have been preterm) was only 2.3 per cent.

According to Schroeder, who analyzed approximately 200,000 cases (1899), the breech presented in 3.11 per cent of near-term pregnancies. In 51,000 deliveries which occured at the New York Lying-In Hospital (1909), the incidence of term breech was 3.9 per cent. Cesarean section at about this time was accomplished in <2 per cent of cases to rescue the mother—rarely the fetus.

Dr. Wolter's reported incidence is much smaller than expected. Hence, I must presume that occasional external version was done and/or that others were "lost" by cesarean section under the classification of fetopelvic disproportion, preeclampsia-eclampsia, etc. This is not a criticism of Dr. Wolter's industry, it simply indicates how difficult it is to obtain actual figures retrospectively.

Breech presentation, scarcely a rarity in human parturition, is classed as an abnormality because of the high associated perinatal mortality and morbidity rates and the slightly increased maternal morbidity. Our specialty has jousted with this problem now for two generations, at least, attempting one approach or another to reduce the "high price" paid by the offspring for this particular entry. External version, with or without anesthesia, and cesarean section, with or without labor, have been discussed heatedly by the membership of this Society upon numerous occasions without resolution of the problem. No subject in obstetrics is more seriously debated by the so-called conservatives vs. the progressives than breech delivery.

External version was never popular in North America although this is to be regretted because it is really effective as Campbell, as well as Turko, and lately Rainey have individually demonstrated. Certainly, external version will reduce the need for cesarean section as it may have in this series.

Zatanuchi and Andros have proposed a prognostic scoring index which, although incomplete (no mention of pelvimetry), offers some help. Nonetheless, it was only occasionally used by Dr. Wolter's associates. The same can be said for x-ray pelvimetry.

Because there can be no true trial of labor in breech presentation, one must utilize other prognostic criteria, e.g., ultrasonography or roentgenography of the fetal head *and* pelvis—often a complicated and impractical exercise. Or one may become committed to delivery from below on the basis of other favorable auguries, etc., previously successful delivery of an "averaged-size" fetus from below through an ample pelvis with good labor. All of these are "guestimates," however, and are completely unscientific directives for the

management of a medium or high-risk fetus. Even the advantages of the Brandt maneuver over the Mauriceau-Smellie-Viet maneuver may be lost if there is cephalopelvic disproportion or extension of the aftercoming head.

A cesarean section rate of 21.9 per cent (inclusive) is not truly meaningful for comparison with vaginal delivery of the breech here. Cesarean section is not innocuous, as we all know, although elective cesarean section carries extremely low maternal and perinatal mortality and morbidity rates.

These comments are not meant to be ultracritical but are offered to indicate that, although it appears that even routine cesarean section is better than any type of breech delivery, we do not really know how much better it is and whether the "price is right." Many centers (our own included) are engaged in prospective studies to clarify these and other points at issue.

My main problem has been Dr. Wolter's and my own inability to come to grips with many of the related problems using the data available. There was no plan or specific policy regarding breech delivery at Overlake Hospital. (This may be impossible in a general hospital, however.) Hence, one cannot evaluate case management, e.g., no data are available regarding total breech extraction vs. assisted breech or cesarean section after labor vs. elective cesarean section. True, four out of five perinatal deaths (a very good record) could have been prevented by elective cesarean section. One perinatal death (RDS) followed cesarean section, however, Moreover, when we recall that of the 23 perinatal morbidity cases (5.7 per cent) (also excellent) there were nine serious neonatal problems all of which could have been avoided by cesarean section, it is very easy to vote the straight cesarean section ticket. However, external version had been practiced in one group but not in another, for example, this might have provided something really tangible to compare.

So, we have a number of varying results over a 12 year period quite without a bench mark, baseline, or actual comparison group essential for assessment. True, things are getting better at Overlake, but why and how much?

Cesarean section may be the reason, but under what circumstances? Should cesarean section be done for the delivery of all primigravid breeches at term? If the answer is yes, why not for all breeches at or about 40 weeks? If the answer is no, is there a good reason for this position?

I am unhappy with cesarean section as a "blind" solution to breech presentation. I say this not because of stubbornness, but because we seem to have skipped a number of essential steps in our thought processes to date. I fear it will take a much different and larger study than this one to answer my questions. Dr. Wolter has not helped my "unease" but I am most grateful to him for trying.

DR. EDMUND F. ANDERSON, San Francisco, California. I wish to add a footnote to Dr. Wolter's paper, with full realization that I probably will be labeled "old fashioned." Recently I had two breeches close together, assisted at each delivery by a first- or second-year resident, and Dr. Wolter mentioned the fact that the great danger to the fetus comes at the time of delivery rather than during labor. I discovered that these fellows knew practically nothing about breech delivery. They assumed that every breech was going to be delivered by cesarean section, and when it came to the delivery they knew nothing about getting the arms out, about delivering the after-coming head, the use of Piper forceps, or any such things. Their first thought was—a breech; we do a cesarean.

It seemed to me that that was too much science and not enough art. They knew all about ultrasonic monitoring, scalp sampling, all the ultrascientific things, but nothing about the actual technique and art of delivering a breech.

DR. CARL GOETSCH, Berkeley, California. Obsessed as I am with problems of professional liability, I cannot help but think of the implications of this problem of the management of breeches to that problem.

If you look at the high-cost incidence of malpractice actions, a very large percentage involve neonates, the results of accidents at delivery, and defects that are blamed on birth injury but which we now know are really accidents during the prenatal development in utero. I think that society is going to be ever more demanding on us in the management of procedures such as breech presentation where we have cesarean section, for instance, which the public looks upon as the answer to everything, even though it may not be.

I was reminded, while listening to the paper, that there is a development coming across the nation of regionalization in respect to high-risk obstetric problems. I was just last week in Rochester where the new regional center at the medical school was recently opened. It has met with a very prompt and tremendous response. The doctors of the entire region are very cooperative in sending their high-risk problems to the university, where they have all kinds of fancy monitoring equipment and so on. This, I think, offers a very promising solution to some of these problems such as the breech, unless it is a breech that is unexpected.

DR. WOLTER (Closing). I can only say that we did feel very much as Dr. Benson did, a certain amount of frustration that a series like this certainly does not answer questions or tell us exactly what is the best route to go.

During this 12 year period the cesarean section charts were also reviewed to look for hidden cases of breech presentation that might have been mislabeled and this 2.3 per cent term breech rate is the rate after exclusion of nonrelated cases of perinatal deaths and repeat cesarean sections. I use the same exclusions as Johnson did in his series of 500 cases of term breech from the Mayo Clinic. I think that the 2.3 per cent rate

is in the same ball park with others. There were several references to external version noted in many prenatal records. However, I did not see the prenatal records where external version had been successful as these cases delivered as vertex.

There were 401 of the 402 charts available for perusal. All of these 401 charts had the prenatal record. There was one chart missing. However, the office records in this particular case included several of the copies of hospital records, so that the 402 cases were fairly well documented. I certainly share Dr. Benson's feeling that we have no way of telling if cesarean section could answer all of our questions, or solve all of our problems.

In response to Dr. Anderson, I feel that among practicing obstetricians there is also inability to maintain skill level at delivery of breech infants. There was one physician on our staff who was present when the hospital opened and has remained very active throughout this period. He delivered some 50 of these 400 cases. However, there were no other physicians who delivered any significant number. I wish to point out that many physicians on our staff are also on staffs at other hospitals so that their total breech experience perhaps is spread over several hospitals.

One of the members of our staff, who is also a member of this Society, was kind enough to look at my material for me, and he pointed out the same thing that Dr. Goetsch points out—that the professional liability problem perhaps is very heavily weighted in deciding which way to deliver the infant. We also feel in our community that high-risk cases will more and more be managed at the university, which is only 10 miles away.

The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy

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Data on the outcome of pregnancy are based upon a prospective study of 14,833 single births to women whose blood pressures during the fifth and sixth months of gestation were recorded. With each 5 mm. Hg rise in the mean arterial pressure (MAP) there is a progressive increase in the perinatal mortality rate. At each MAP level, the stillbirth rates and neonatal mortality rates are higher in blacks than in whites. When middle-trimester MAP is 90 mm. Hg or more, there is a significant increase in (1) the stillbirth rate, (2) the frequency of proteinuria, hypertension, and diagnosed pre-eclampsia in the third trimester, and (3) the frequency of intrauterine fetal growth retardation. We believe that all of these events are due to an impaired uteroplacental circulation, with which elevated blood pressures are associated. Women who have an average MAP of 90 or more during the fifth and sixth months should be considered in a high-risk category.

NUMEROUS studies pertaining to the behavior of the blood pressure during pregnancy have been published, and there is general agreement that the lowest levels, at least of diastolic pressures, are noted during the middle trimester. Clinical attention, however, has been focused mainly upon third-trimester blood pressures or the rises of blood pressure during late pregnancy, especially when accompanied by proteinuria or edema. The purpose of this communication is to direct attention to the levels of blood pressure observed during the middle trimester and to relate these to the outcome of pregnancy for both the mother and her fetus.

The impact which any given blood pressure has upon circulatory dynamics is probably best expressed by utilizing the mean arterial pressure (MAP). This also has the advantage of working with a single figure which may be readily derived from the systolic and diastolic readings. The most commonly used formula is that advocated by Burton[1]:

$$MAP = \frac{S + 2D}{3}$$

which may be converted to a simpler formula for clinical use, namely, MAP is equal to the diastolic pressure plus one third of the pulse pressure. It is generally accepted that such blood pressure permutations as 120/60, 100/70, or 110/65, all of which are equal to a MAP of 80 mm. Hg, have the same physiologic significance insofar as the head of arterial pressure is concerned. A simple nomogram for reading MAP from the systolic and diastolic pressure is shown in Fig. 1.

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Material and methods

The accumulated data are derived from observations on the obstetric population studied during the years 1959 to 1967 by the Child Health and Development Studies which were initiated by the late Dr. J. Yerushalmy in Oakland, California. The patients were members of the Kaiser Foundation Health Plan, a prepaid medical care program in the San Francisco—East Bay Area. The nature of this population and details of the study were described in a prior publication by van den Berg and Yerushalmy.[2]

This study is based upon nearly 15,000 women whose pregnancies terminated in single live births or stillbirths more than 180 days after the onset of the last menstrual period, and for whom one or more blood

pressure readings taken between 121 and 180 days are available. During this 60 day interval, the latter 2 months of the middle trimester, 77 per cent of the population had two or more blood pressure measurements recorded for them. All readings taken in this interval for each pregnancy were averaged to generate a second-trimester mean arterial pressure (MAP-2). This period was chosen because blood pressures are at their lowest levels at this time and, in addition, the majority of women are under observation at this stage of pregnancy. This measurement can thus be analyzed for its predictive value.

The blood pressure measurements used in this analysis are typical clinic measurements. Such measurements are subject to both individual and observer variability, but the large number of women observed serves to minimize the influence of the inherent variability on the analysis. In addition, a high blood pressure recorded at any visit was retaken; thus enhancing the reliability of readings falling in the higher MAP categories.

Our data compare and contrast the observations for blacks and whites. We have also included the results for all ethnic groups; this term, in addition to the blacks and whites, includes others, predominantly Orientals and Mexican Americans.

In order to examine the correlation between early and late blood pressures, the blood pressure attained in the third trimester is expressed as the mean of the two highest mean arterial pressures recorded after 180 days' gestation. If the pregnancy terminated before two blood pressure measurements were taken in the third trimester, this value, MAP-3, was designated as unknown. It should be pointed out that the mortality rates shown in the tables are not directly comparable with other studies in that only pregnancies extending into the third trimester and for which MAP-2 values are known are considered. Furthermore, pregnancies terminating early in the third trimester before two blood pressure measurements had been recorded are excluded from tables involving MAP-3.

Results and comment

Mean arterial pressure during pregnancy. A typical curve for MAP during gestation (Fig. 2) is based upon single term births in nulliparous white women, 25 to 34 years of age. The curve is lower for multiparous women, higher for blacks, and lower for oriental women. The differences due to parity have been described in a separate communication.[3] Ethnic differences in blood pressure during pregnancy were also observed by MacGillivray and associates.[4]

The relationship between middle-trimester and third-trimester MAP values is shown in Fig. 3. For each ethnic group, as MAP-2 increases so does MAP-3. The per cent distribution of the white and black populations according to their MAP-2 values is shown in Table I. It should be noted that 6.6 per cent more blacks than whites fall into the range of 85 mm. Hg or greater. The differences between the distribution for blacks and whites are highly significant.

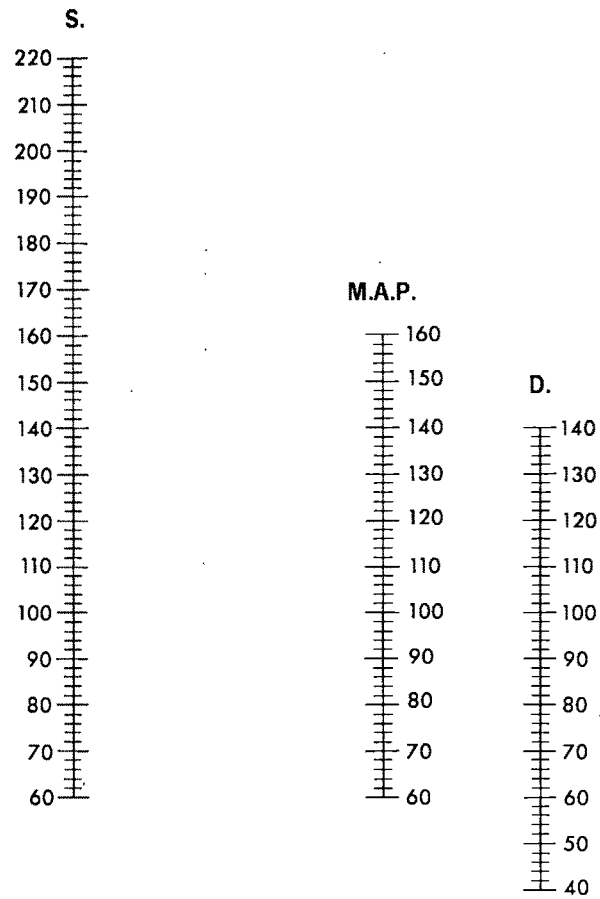


Fig. 1. Blood pressure nomogram.

Middle-trimester blood pressure and perinatal mortality rates. The fetal outcome in 14,833 single births of all ethnic groups at various levels of mean arterial pressures during the middle trimester is shown in Table II. The rates are also shown for whites and blacks separately. There is a progressive rise in the stillbirth rate, with a distinct break occurring at 90 mm. Hg. In terms of fetal loss, mean arterial pressures of 90 mm. Hg or more, even though not considered hypertensive per se, must be regarded as ominous when observed in the middle trimester. The neonatal death rate was not appreciably affected in that no consistent pattern is shown.

Dividing MAP-2 into two groups at 85 mm. Hg, thus combining those with borderline and high MAP-2



Fig. 2. Mean arterial pressure by gestational age for single white term live births (nulliparas, 25 to 34 years of age). Some gravidas were not under observation prior to the twentieth week after LMP.

Table I. Frequency and per cent distribution of MAP-2, by ethnic group

	*White**		*Black**		*All ethnic groups*	
MAP-2	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
< 75	2,228	21.8	617	20.7	3,377	22.8
75-79	2,235	21.9	570	19.1	3,185	21.5
80-84	2,558	25.1	664	22.3	3,580	24.1
85-89	1,848	18.1	595	20.0	2,677	18.0
90-94	916	9.0	324	10.9	1,328	9.0
≥ 95	424	4.2	209	7.0	686	4.6
Total	10,209	100.0	2,979	100.0	14,833	100.00

*The distributions are significantly different by χ^2 ($p < 0.001$).

values, the influence of elevated blood pressure upon the stillbirth rate is seen to be markedly exaggerated in black women, as shown in Table III. Whereas the relative increase of stillbirth rates in white women was 58 per cent, that for black women was 112 per cent, or nearly double. By contrast, the over-all relative effect of elevated pressures during the fifth and sixth months in terms of perinatal death is similar for whites and blacks, although the absolute rates for blacks are considerably higher.

MAP-2 and fetal growth rate. One delicate index of a deleterious effect upon fetal growth rate is the frequency of small-for-gestational-age (SGA) infants, defined here as live births born at 37 or more weeks of gestation and weighing 2,500 grams or less. As shown in Table IV, there is a slight decrease in the frequency of SGA infants as the middle-trimester MAP increases from below 75 up to 80 mm. Hg. Then there is an increase with MAP-2 pressures of 90 or more. There is a further increase when significant proteinuria occurs, irrespective of blood pressure levels. The SGA infant rates are 6.0 per cent for white and 8.6 per cent for black populations with proteinuria. This supports the clinical opinion that hypertension alone or significant proteinuria alone (probably representing renal disease) affects fetal growth adversely.

The higher incidence of SGA infants at the low MAP-2 values as contrasted with the moderate MAP-2 values is not explained, but might possibly be related to body build of the gravidas in that slender gravidas tend to have both lower blood pressures and smaller babies. An alternative explanation might be that a minimal head of arterial pressure is required for optimal uteroplacental flow.

As the middle-trimester blood pressure increases from 85 to 89 mm. Hg to 95 or more, the increase in the per cent incidence of growth retarded infants almost precisely parallels the increase in the relative frequency of stillbirths in both white and black women. We believe that both events are related to a common denominator, namely, a progressive impairment of the uteroplacental circulation which, in turn, is associated with a progressive increase in the mean arterial pressure.

Mid-trimester blood pressure and the development of proteinuria, clinical pre-eclampsia, or hypertension. Significant proteinuria (2 plus or more) developed in 1.7 per cent of the white and 2.5 per cent of the black populations. Sharp increases in the rates of proteinuria were not observed until the middle-

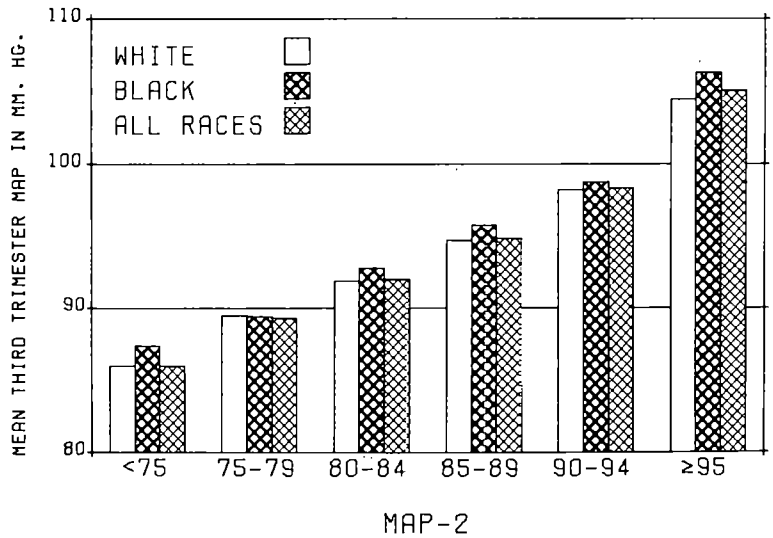


Fig. 3. Mean third-trimester MAP for each MAP-2 interval by race.

Table II. Stillbirth and neonatal death rates by MAP-2 and ethnic group

	Third-trimester stillbirths per 1,000 total births			*Neonatal deaths per 1,000 live births*		
MAP-2	*White**	*Black**	*All ethnic groups*	*White†*	*Black†*	*All ethnic groups*
< 75	8.5	8.1	9.2	6.8	21.2	10.2
75-79	10.7	12.3	10.7	12.7	12.4	12.7
80-84	10.9	18.1	12.3	9.9	19.9	11.3
85-89	13.0	18.5	14.2	9.3	13.7	9.9
90-94	15.3	21.6	18.8	13.3	12.6	13.8
≥ 95	30.7	62.2	37.9	7.3	15.3	15.2
Total	12.0	18.5	13.3	9.9	16.4	11.5

*Daniel's Test for Trend is significant, $p < 0.01$.[5, 6]

†Daniel's Test for Trend is not significant.

Table III. Stillbirth and perinatal mortality rates for MAP-2 <85 and ≥85 and their ratios, by ethnic group

	Third-trimester stillbirths per 1,000 total births			*Perinatal deaths per 1,000 total births*		
MAP-2	*White*	*Black*	*All ethnic groups*	*White*	*Black*	*All ethnic groups*
<85	10.1	13.0	10.7	19.8	30.8	22.0
≥85	16.0	27.5	19.0	26.0	40.8	30.5
Ratio ≥85 : <85	1.58	2.12	1.78	1.31	1.32	1.39

trimester MAP exceeded 95 mm. Hg but for all ethnic groups combined a slight but steady increase in significant proteinuria is noted as MAP-2 increases (Table V). The development of a trace or 1 plus proteinuria is also seen to have an increasing trend. Proteinuria developed more often in nulliparous patients than in multiparous patients at all MAP-2 levels.

The clinical diagnosis of pre-eclampsia prior to hospital admission was based upon the combination of hypertension with proteinuria and/or generalized edema. The diagnosis was recorded in 4.0 per cent of nulliparas and 2.2 per cent of multiparas. When grouped according to the mean arterial pressures in the middle trimester (Table VI), it is readily apparent that when the MAP-2 is 85 mm. Hg or higher the groups have an incidence of pre-eclampsia that is higher than average, but it should be noted that there is a steady progression in the incidence of pre-eclampsia with each increment of MAP-2. There is, of course, a dramatic increase in the group of MAP-2 with 95 mm. Hg or more, a group which no doubt represents chronic hypertension.

Whereas the clinical diagnosis of pre-eclampsia may be subject to some variation of interpretation among the obstetricians involved in the prenatal care, there would be little disagreement about the diagnosis of hypertension when the mean of the two highest recordings in the third trimester reaches a MAP of 110 mm. Hg or more. Once again, the incidence of hypertension defined in this way increases rapidly as the mid-trimester mean arterial pressures increase, and this incidence is also greater in the black women than in the white women (Table VII).

A high prevalence of hypertension among the blacks in this country as contrasted with the whites is well

Table IV. Per cent incidence of small-for-gestational-age infants* by MAP-2 and ethnic group

MAP-2	*White†*	*Black†*	*All ethnic groups*
<75	2.2	4.1	2.6
75-79	1.9	2.1	2.0
80-84	1.7	2.3	1.9
85-89	1.4	2.4	1.7
90-94	2.9	4.1	3.1
≥95	3.2	6.1	4.2
Total	2.0	3.1	2.3

*Single live births weighing <2,500 grams at gestations ≥37 weeks.

†The relationship between MAP-2 and the proportion of SGA infants is significant by χ^2 ($p < 0.05$).

Table V. Per cent distribution of proteinuria in the third trimester at each MAP-2 level for all ethnic groups

	Proteinuria		
MAP-2	*2 plus or more**	*Trace or 1 plus*	*None*
<75	1.2	20.0	78.7
75-79	1.4	23.3	75.4
80-84	1.8	26.3	72.0
85-89	2.0	25.8	72.2
90-94	2.3	30.0	67.7
≥95	5.4	31.6	63.0
Total	1.8	24.7	73.5

*Daniel's Test for Trend is significant ($p < 0.01$).[5, 6]

established. In the National Health Survey the prevalence rate of definite hypertension was more than three times greater for black women 18 to 24 and 25 to 34 years of age than for the corresponding white women.[7] Thus it is not surprising to find a higher proportion of black gravidas in the high MAP-2 categories.

The precise reasons why more black gravidas are found in each category of elevated blood pressure are not known, but may be related to (1) a higher sodium intake, (2) a greater frequency of obesity, or (3) a higher frequency of environmental "stress." Nevertheless, it is clear from the data presented that a large proportion of the excess stillbirths occurring among the black women are associated with the various forms of hypertension which occur in pregnancy.

Conclusions

The use of mean arterial pressure (MAP) simplifies the interpretation of blood pressure recordings during pregnancy. The MAP reaches its lowest level in the middle trimester and then steadily increases until term.

When the average of MAP readings taken during the fifth and sixth months of pregnancy is 90 mm. Hg or more, there is a significant increase (1) in the stillbirth rate, (2) in the frequency of intrauterine fetal growth retardation, and (3) in the frequency of proteinuria, hypertension, and diagnosed pre-eclampsia in the third trimester. All of these events occur more often in the black race than in the white race at each level of elevated blood pressure. A higher percentage of black women are also found in each of the elevated blood pressure categories.

Obstetric patients who are observed to have mean arterial pressures of 90 mm. Hg or more prior to 26 weeks of gestation should be considered in a "high-risk" category.

We believe that elevated blood pressure may be associated with an impaired uteroplacental circulation, and that the latter may form a common denominator for both stillbirth and intrauterine growth retardation.

Table VI. Per cent incidence of diagnosed pre-eclampsia by MAP-2 and ethnic group

MAP-2	*White**	*Black**	*All ethnic groups*
<75	0.9	0.8	0.7
75-79	1.2	1.6	1.2
80-84	1.5	3.8	2.0
85-89	3.0	5.2	3.4
90-94	5.0	6.2	5.6
≥95	12.5	18.7	14.6
Total	2.3	4.3	2.7

*Daniel's Test for Trend is significant ($p<0.01$).[5, 6]

Table VII. Per cent of gravidas with third-trimester MAP equal to or greater than 110 by MAP-2 and ethnic group.

MAP-2	*White**	*Black**	*All ethnic groups*
<75	0.2	0.7	0.3
75-79	0.4	0.4	0.4
80-84	0.9	2.0	1.0
85-89	2.5	4.0	2.8
90-94	6.0	7.1	6.5
≥95	22.0	33.8	25.9
Total	2.2	4.6	2.7

*Daniel's Test for Trend is significant ($p<0.01$).[5, 6]

The authors wish to thank Mr. Harald Kipp, who did the computer programming for this analysis.

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Discussion

DR. KENNETH R. NISWANDER, Davis, California. A relationship between the hypertensive diseases of pregnancy and an increase in the perinatal death rate has long been recognized. The data of Page and Christianson suggesting that the level of hypertension at which this ill effect occurs is much lower than we have previously thought represent a new idea, however. Furthermore, the suggestion that this bad effect can be predicted when slight increases in "normal" blood pressure occur in the *middle trimester* is even more startling. The data presented by Dr. Page are convincing and his conclusions cannot be seriously questioned. Indeed, unpublished data from the Collaborative Perinatal Project confirm Dr. Page's data almost precisely.[1] Assimilation of these new ideas into clinical practice will be difficult, if not impossible, with older terminologies of the hypertensive diseases associated with pregnancy. Would any clinician label a patient with an "elevated" blood pressure of 120/76 mm. Hg during the second trimester a chronic hypertensive subject or suggest that she is suffering from acute toxemia of pregnancy? I think not. What "label" or diagnosis would Dr. Page attach to such a patient? One is certainly needed if the ill effects of this "hypertension" are to be acknowledged and prevented or treated.

Dr. Page has added another factor to the long list of pregnancy or perinatal causes of an increase in the perinatal mortality rate. The pathophysiologic effect of many of these factors can be easily explained and understood. The intrauterine hypoxia suffered by a fetus with umbilical cord prolapse will obviously cause fetal death if the hypoxia is not relieved quickly. In like manner, maternal starvation, if severe, will deprive the fetus of essential nutrients. The mechanism by which hypertensive disease deprives the fetus of maternal support, however, is somewhat more complex and less easily explained.

Assali and Brinkman[2] pointed out that blood pressure is related primarily to cardiac output and vascular resistance. During pregnancy cardiac output is known to increase, and it can be presumed that peripheral vascular resistance must decrease since no rise in blood pressure has been noted during pregnancy, at least until near term. The flow of blood through the placenta depends on the perfusing system. Increasing the pressure, at least in the sheep, increases the uteroplacental blood flow in a linear fashion. Why then should hypertensive disease have a deleterious effect on the fetus?

Assali has further taught us that these relationships hold only if the adrenergic system is not activated. Stimulation of the adrenergic system will adversely affect the uteroplacental blood flow. To explain the bad effect of hypertensive disease, therefore, we must presume such an activation in the patient.

If the relationship between a slight increase in MAP in the middle trimester and a decrease in fetal survival can be accepted, how can we prevent or reverse this effect? In short, what treatment might be useful? Certainly, the very least we can do is to label such a patient "high risk" and begin periodic evaluations of fetoplacental function at 26 weeks' gestation or whenever appropriate. Urinary estriol levels and repeated OCT's are the best tools presently available for this purpose. Delivery when the fetus is found to be mature by amniotic fluid L/S ratios or other tests or when the fetoplacental function shows signs of failing is indicated. Such an approach, however, treats the symptom and not the disease. Can we treat the disease or prevent it and thus eliminate the deleterious fetal effects?

Would Dr. Page care to speculate on the possibility of "deactivating" the adrenergic system with a drug—a sedative perhaps? Or does he think a vasorelaxing drug might prevent vasospasm even if adrenergic substances are released? Would bed rest increase placental blood flow sufficiently to make a difference? In the past he has suggested the possibility of feeding the fetus who is malnourished in utero. Is such a suggestion a reasonable one in the "disease" he describes in his paper? In short, now that he has identified the problem, does he have advice for us on how to avoid it or minimize its effects?

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DR. EDWARD J. QUILLIGAN, Los Angeles, California. Does Dr. Page know in what position these blood pressure readings were taken? Were the patients in the lateral or the supine position? Because we know there are about 10 per cent of patients who do become

hypotensive in the second trimester of pregnancy in the supine position, and there are also, according to Gant and his co-workers, a significant number of patients who will demonstrate a reactive hypertension in the late second trimester. Those are the ones that he believes will become the pre-eclamptic patients. Finally, I would like to have Dr. Page comment on what he thinks is the best position if we are going to use this as a diagnostic tool.

DR. BOYD C. QUINT, Seattle, Washington. I wonder if you might be able to approach the question of blood volume relation to toxemia from the other direction. We see a number of patients in pregnancy whose hematocrit fails to stay up despite adequate iron intakes. We had occasion to study some of these patients in the last few years and with radioactive chromate studies found that they had a markedly increased plasma volume, with normal total red cell mass for programming. If enough of these women could be identified I wonder if we could demonstrate a lowered incidence of toxemia in this group of patients?

DR. PAGE (Closing). I am pleased to learn that unpublished data from the Collaborative Project support the conclusions we have drawn.

You asked about how we would label the various groups. If the average of mean arterial pressures during the fifth and sixth months exceeds 90, but the two highest readings in the third trimester are below 105, we call those patients "borderline hypertensives." If they also demonstrate hypertension in the third trimester we call them "chronic hypertensives." If significant proteinuria develops, however, we use the term "pre-eclampsia."

Insofar as treatment of middle-trimester hypertension is concerned, I can only suggest the employment of additional rest, the avoidance of vigorous exercise perhaps, the reduction of stress factors when possible, and the use of mild sedation. With higher levels of blood pressure, one might consider the use of oral antihypertensive drugs, but not diuretic drugs, because we believe that these increase the perinatal mortality rates.

Regarding the method of taking blood pressures, these were almost all taken by the clinic nurses with the patients sitting. Hypertensive readings, however, were repeated after the patient rested in the lateral recumbent position.

Severe pre-eclampsia: Another great imitator

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Twenty-eight women with severe pre-eclampsia were misdiagnosed and initially thought to have disorders unrelated to pregnancy. Their chief complaints included failing vision, liver or gallbladder dysfunction, renal failure, hemorrhage, seizures, and heart failure. Laboratory studies usually demonstrated thrombocytopenia and high hematocrit values. The development of these symptoms appears to begin with failure of the primigravida to appropriately increase her blood volume commensurate with the increase in size of her uterus. Expanding the severely pre-eclamptic patient's blood volume with intravenous albumin appears to be an effective and appropriate therapy.

THOUGH pre-eclampsia appears to be occurring with decreased frequency in our community, we continue to see the severe form, which often has bizarre and confusing symptoms. Some of these unusual patients have been incorrectly referred to other specialties by members of our obstetric staff. Listed below are some of the symptoms and laboratory findings of 28 such women who initially were thought to have an acute illness unrelated to pregnancy, but who in all likelihood had only severe pre-eclampsia.

Material and findings

Seventeen of the women were admitted to either the Santa Clara Valley Medical Center, San Jose, or to the Stanford University Hospital, Stanford, California. Nine were hospitalized in other local hospitals and the remaining two were seen in consultation in Honolulu. Several of these cases became apparent because of unexpected elevations of screening serum glutamic oxalacetic transaminase (SGOT) values or because of reports of decreased platelets on peripheral blood smears.

The records of 20 other women admitted to Santa Clara Valley Medical Center of Kaiser Hospital, Santa Clara, with a diagnosis of severe pre-eclampsia not in labor with typical symptoms and 20 primigravidas at 34 to 36 weeks were reviewed (Table I). These were compared with the study patients as well as with normal primigravidas at 32 to 37 weeks of pregnancy.

Although the first group of women (Table II) demonstrated well-recognized pre-eclampsia symptoms, their chief complaint was unusual and dramatic, and they were therefore referred to other specialties for primary care. In the one case in this group in which platelets were recorded as normal (B-6), there was a high hematocrit and the patient improved dramatically after intravenous albumin therapy. Consultation was given for the case of gastrointestinal hemorrhage because of concern over the relationship of a dead fetus, thrombocytopenia, and abnormal bleeding. She had bleeding from no other site, normal prothrombin and fibrinogen levels, responded to toxemia therapy, and recovered completely with termination of her pregnancy.

The second group of women (Table III) had the more unusual symptoms of pre-eclampsia which included those with right upper quadrant pain associated with liver dysfunction (Section D), and those with seizures but apparently no other striking signs of pre-eclampsia (Section E). Patients D3-6 and E2 were initially referred for surgical consultation; Patients D1-2 were isolated for "hepatitis." Those with a diagnosis of epilepsy were treated as such.

Brief case histories of the last group of patients are presented because their diagnosis of severe pre-eclampsia is even more argumentative than the preceding cases.

Case histories

G. Admission diagnosis of idiopathic thrombocytopenia purpura (ITP). A. C., a 22-year-old black woman, para 0-0-0-0, had ITP diagnosed at 22 weeks' gestation. The platelet count was 19,000 and the

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Table I. Comparison of blood SGOT and platelet values in normal and pre-eclamptic primigravidas

	Normal pregnancies	*Severe pre-eclampsia*	*Present series**
No. of cases	20	20	25
SGOT (units/ml.)	31 ± 19† (10 – 95)‡	56 ± 31 (21 – 170)	91 ± 43 (42 – 203)
Platelets (thousands per mm.^{3})	210 ± 81 (107 – 361)	143 ± 41 (83 – 188)	101 ± 47 (58 – 165)

( ) = range
± = SD
*Women with ITP were excluded.
†± Standard deviation.
‡Numbers in parentheses indicate range.

Table II. Misdiagnosis of severe pre-eclampsia

	Admitting diagnosis	*Weeks pregnant*	*Infant at discharge*	*BP*	*Hct.*	*Platelets*	*Liver function*
A. Eye:	Retinal hemorrhage*	30	Alive	170/110	44	93,500	SGOT↑
	Hysteria	27	Dead	130/96	42	Decreased	—
	Retinal detachment*	31	Alive	165/108	39	Decreased	SGOT↑
B. Renal:	Acute golmeruler hephritis	28	Dead	140/100	42	65,000	SGOT↑
	Acute renal failure*	32	Dead	130/86	44	52,000	SGOT↑
	Hypertension*	24	Dead	160/120	48	40,000	SGOT–
	Nephrosis	24	Dead	140/88	46	Decreased	—
	Nephrosis*	37	Alive	120/78	44	87,000	SGOT↑
	Nephrosis*	29	Alive	150/90	45	Normal	—
C. G.I.:	Upper GI bleeder	27	Dead	130/82	32	46,000	SGOT↑

*Given intravenous salt-poor albumin.

Table III. Misdiagnosis of severe pre-eclampsia

	Admitting diagnosis	*Weeks pregnant*	*Infant at discharge*	*BP*	*Hct.*	*Platelets*	*Liver function*
D. Liver:	Hepatitis*	32	Alive	150/110	38	94,000	Bili↑ SGOT↑
	Hepatitis	29	Dead	140/90	44	68,000	Bili↑ SGOT↑
	Cholelithiasis	31	Dead	138/90	46	Normal	SGOT↑
	Cholelithiasis*	33	Alive	144/80	38	Decreased	Bili↑ SGOT↑
	Appendicitis	30	Dead	150/92	42	94,000	SGOT↑
	Pancreatitis	34	Alive	150/100	43	76,000	SGOT↑
E. CNS	Seizure	27	Dead	130/60	48	Decreased	SGOT–
	Brain tumor	25	Dead	140/100	40	Normal	SGOT↑
	Epilepsy	27	Dead	150/100	42	92,000	SGOT↑
	Epilepsy*	32	Alive	148/94	41	53,000	—
F. CNS:	Epilepsy	Post partum	Alive	160/100	34	Decreased	SGOT↑
	Epilepsy	Post partum	Alive	134/92	41	84,000	—
	Epilepsy	Post partum	Alive	150/80	44	69,000	SGOT↑

*Given intravenous salt-poor albumin.

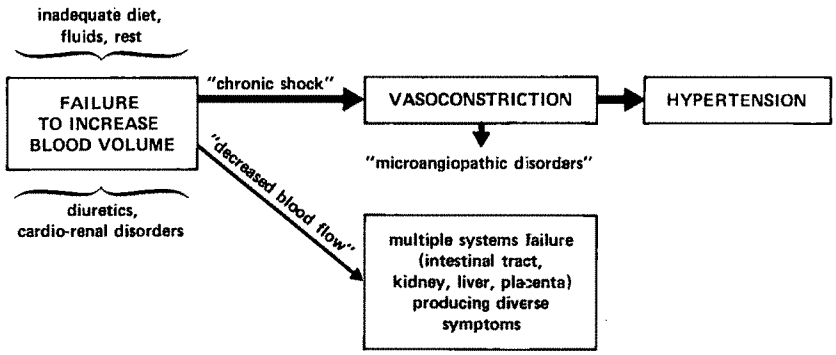


Fig. 1. Development of symptoms of severe pre-eclampsia.

Table IV. Misdiagnosis of severe pre-eclampsia as heart failure

Weeks pregnant	*Infant at discharge*	*HCT*	*Platelets*	*Comment*
32	Alive	46	73,000	Became hypertensive after cardiac failure was corrected
38	Dead	44	120,000	After fetal death, had seizure; B/P 170/110 post partum, heart failure cleared third day post partum, subsequent pregnancy uneventful

patient was treated with steroids. (Initial impression had been microangiopathic disorder, but patient had no other symptoms of DIC or even pre-eclampsia.) At time of delivery at 40 weeks' gestation, the platelet count was 75,000 and the patient had acute pre-eclampsia (BP 170/100 with severe clonus). The newborn infant's lowest platelet count was 55,000 and he did well.

I. L., a 24-year-old Oriental woman, para 0-0-0-0, with diagnosis of ITP made at 32 weeks' gestation, was treated with steroids. Spontaneous labor and vaginal delivery of triplets occurred at 36 weeks' gestation when her platelet count was 4,000 and her BP was 170/110. The patient had a postpartum hemorrhage and two grand mal seizures. The mother and all the infants (despite platelet counts below 10,000) subsequently did well.

P. O., a 19-year-old Oriental woman, para 0-0-0-0, had ITP diagnosed at 18 weeks' gestation (platelets 56,000) and was treated with steroids. During labor at term, the platelet count was 126,000 and her BP was 160/110. Patient and infant (normal platelet count) did well.

The misdiagnosis of severe pre-eclampsia as heart failure is shown in Table IV.

Comment

These pregnant women presented symptom complexes which have previously been described as representing severe pre-eclampsia (Table V). Yet either because the classical symptoms of pre-eclampsia were inconspicuous or because the chief symptoms were not recognized for what they were, these women were initially all referred to some other specialty for diagnosis and therapy.

Table V. Prior description of some unusual symptoms of severe pre-eclampsia

Symptom	*Author(s)*	*Year*
GI bleeding	Carazelo, Efstatin[1]	1948
	Langmade[2]	1950
Heart failure	Teel, Reid, Hertig[3]	1937
Hemoconcentration	Zangemeister[4]	1903
Liver disease	Verhage[5]	1940
Thrombocytopenia	Nielsen[6]	1969
Visual disorders	Wagener[7]	1933

The bases for selection of the cases in this report were that they be primigravidas and have unusual symptom complexes, thrombocytopenia, increased hematocrit and SGOT values, and BUN values above 10 mg. per 100 ml., at least one of the generally recognizable signs of toxemia, and that they had

recovered with termination of their pregnancy. We have observed a high incidence of decreased platelets among women with severe pre-eclampsia, but Pritchard and associates,[8] after a large clinical experience, reported that only 26 per cent of women with eclampsia had platelet counts below 150,000. If this is accurate, this report will survey only a portion of the problem as many others with severe pre-eclampsia whose symptoms mimic other diseases will have been missed because of their normal laboratory findings. But aside from re-emphasizing their unique symptoms, it still appears worthwhile to discuss these patients because their clinical and laboratory findings also suggest a common pathophysiology for at least many cases of severe pre-eclampsia.

In the English literature alone, there are three recent treatises on the pathophysiology of pre-eclampsia[9–11] as well as repeated discussions of the concepts of Brain and associates[12] on the associated microangiopathic disorders and those of McKay[13] on disseminated intravascular coagulation (DIC). In explaining the wide variety of symptoms described in this paper, it was easy to derive concepts of responsible mechanism from these sources.

As shown in Fig. 1, the proposed development of symptoms of severe pre-eclampsia begins with the failure of the primigravida to appropriately increase her blood volume commensurate with the increase in size of her uterus.[14, 15] This relatively reduced blood volume is considered to be analogous to chronic shock[16] and leads to generalized vasoconstriction which in turn causes dysfunction of vital organs such as kidneys, placenta, and liver. However, if significant increase in mean blood pressure occurs, the blood flow to these vital organs is at least partially maintained and the patient's symptoms are related chiefly to her hypertension. On the other hand, despite the hypertension, significant organ dysfunction may still occur. The patient with severe pre-eclampsia then presents symptoms which are attributed to her liver, intestinal tract, placenta, kidneys, or eyes; hence the "imitation of other diseases."

Besides reducing blood flow to these critical organs, the small-vessel spasm (and/or DIC) leads to the various microangiopathic disorders, including thrombocytopenia and hemolytic anemia. Microangiopathic disorders or blood cell damage due to disorders of small vessels has been considered characteristic of DIC. Yet, others have emphasized the platelet disorder or attempted to separate the coagulation abnormalities associated with pre-eclampsia into its many probable facets.[13, 17, 18] Clinically, it appears that thrombocytopenia may occur in severe pre-eclampsia before a significant destruction of red blood cells and the onset of hemolytic anemia. (The hemolytic aspects of severe pre-eclampsia are generally quickly recognized, and therefore patients with significant hemolysis have not been included in this report.)

Goodhue and Evans[19] stated that the presence of toxemia should exclude a consideration of idiopathic thrombocytopenia purpura (ITP) in pregnancy as the thrombocytopenia is not then "idiopathic." Their single case history in a review of ITP and pregnancy, however, demonstrated the classic symptoms of pre-eclampsia, as have many other primigravidas with ITP discussed in the literature.[20] Even though the patients with ITP presented here had newborn infants with thrombocytopenia (indicating a placental transferable immunologic factor), they have been included in a discussion of severe pre-eclampsia for the following reasons. First, despite comments to contrary,[21] the incidence of the standard variety of severe pre-eclampsia among primigravidas having ITP is high. Second, severe pre-eclamptics have also had an immunologic disorder of their platelets[13] and there is a suggestion of a similar placental transferable platelet factor.[6] Third, termination of the pregnancy has improved the severe pre-eclamptic and often the thrombocytopenia of gravidas with ITP.

We do not always find other indications of microangiopathic disorders when platelets are decreased in pre-eclampsia, and although the concept of a "toxin" is now discredited, toxins have been implicated as a most serious variety of this symptom complex, thrombotic thrombocytopenia purpura (TTP).[21] It has also been demonstrated that "toxins" like alcohol[22] directly produce thrombocytopenia, or that thrombocytopenia may be a manifestation of folic acid deficiency or a host of other factors. The corollary of our experience is that regardless of the etiology of the thrombocytopenia, a platelet count should be done on all cases of true pre-eclampsia. Not that bleeding problems are a likely risk, but that finding a platelet count below 100,000/mm^3 indicates that the pre-eclampsia is indeed severe.

It is obviously important to rule out primary CNS disease in primigravidas with minimal symptoms of pre-eclampsia who have had their first seizure. But to deny the reality of eclampsia by extensive neurologic workup seems inappropriate. Actually, these six women with seizures represent only a fraction of such primigravidas in our community, the others having relatively normal blood values. The older literature refers to cases of "eclampsia without seizures," but appropriately there are no references to "seizures without eclampsia."

There is no way to estimate the incidence of

pregnant women with severe pre-eclampsia whose chief complaint is not of the traditional type. They seem to appear at least as frequently as do women with eclampsia. One pattern that appears frequently in our series as well as those in the literature is the young gravida at 24 to 32 weeks' gestation with mild hypertension and severe right upper quadrant abdominal pain thought to be gallbladder dysfunction or even hepatitis. Invariably, these patients also have evidence at some time of hemoconcentration, liver, and microangiopathic disorders as well as severe pre-eclampsia. The other symptoms described here have a less consistent pattern but also can be diagnosed by laboratory studies showing relatively increased hematocrit, decreased platelets, liver dysfunction, and slightly elevated to a very high BUN.

Reduced blood volume and hemoconcentration have been viewed as ominous signs in the development of severe pre-eclampsia since the time of Zangemeister[4] in 1903. Instead of focusing our attention upon the traditional signs of severe pre-eclampsia (hypertension, edema, and albuminuria), one must give at least some attention to the primigravida's inability to increase her blood volume and its sequelae. In addition to providing an explanation for the diverse symptoms that may occur, there appear to be three other advantages to thinking of severe pre-eclampsia in these terms.

The first is that the reduced blood volume (RBV) concept provides a definition of the severe pre-eclamptic who is truly at risk for silent fetal death. In our own series, fetal death occurred in the presence of high hematocrits (if the pregnancy was not terminated), while a live neonate (even after 3 to 4 weeks' delay) was obtained when the rising hematocrit was reversed with therapy. A RBV concept also indicates onset of the disease in the early second trimester when blood volume fails to increase.

Another advantage of the RBV concept is that it suggests a logical prophylaxis against the occurrence of severe pre-eclampsia. Gravidas can be instructed to consume sufficient proteins and fluids so their blood volumes will increase. Daytime rest in the horizontal position is also recommended. All these are thought to be helpful in expanding or achieving an adequate blood volume necessary for an uneventful pregnancy.[23]

The third feature of the RBV concept is that it adds to the traditional therapy of severe pre-eclampsia (magnesium sulfate and hypotensive drugs), agents directed at expanding blood volume. Intravenous albumin, plasma or low-molecular-weight dextran have produced dramatic improvement in some cases.[24] Albumin therapy, whether given for hypoalbuminemia or pre-eclampsia, and saline when hyponatremia was present, were beneficial for the pre-eclamptic symptoms in the present cases. Unfortunately, controlled studies to confirm these clinical observations do not seem to exist. Any agent (i.e., diuretics) which reduces blood volume is contraindicated in severe pre-eclampsia if this concept is accurate.

In providing prenatal care for the primigravida, concern instead of satisfaction should be felt when the hematocrit rises in the early third trimester, and consideration should be given toward increasing her blood volume. While Pritchard and Stone[25] have shown the imprecise relationship between hematocrit and blood volume during pregnancy, serially increasing hematocrit values may be significant. Dieckmann[26] used hemoconcentration as an index of severity in eclampsia and pre-eclampsia and recommended routine serial hematocrit measurement in the suspected severely pre-eclamptic patient.

Even though these cases represent a small and perhaps a biased sample, it still seems warranted to conclude that severe pre-eclampsia with dysfunction of several systems resulting from hypovolemia remains a problem of present-day obstetrics. This belief is reinforced by the old as well as recent world-wide observations that expanding the blood volume of women with severe pre-eclampsia is just about the only form of therapy (other than termination of the pregnancy) which can reverse the pathologic process.

These types of cases of severe pre-eclampsia with unusual symptoms are often overshadowed by the large number of primigravidas with mild or pseudopre-eclampsia, or by those with the dramatic clinical picture of eclampsia. Nevertheless, the clinical findings of the RBV group offer one more "explanation" of the pathophysiology of at least some cases of severe pre-eclampsia as well as therapy and prophylaxis for all pre-eclampsia. It should also be apparent that the symptoms of severe pre-eclampsia may not be those typical ones described in textbooks.

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Discussion

Dr. Edward J. Quilligan, Los Angeles, California. Dr. Goodlin, as always, has presented a very provocative paper emphasizing some of the erroneous diagnoses given to patients with hypertensive vascular disease in pregnancy and its complications. This group, many of whom had high hematocrits, low platelets, and abnormal liver function tests, has formed the basis for an interesting discussion of one of his favorite concepts, namely, that in this situation reduced blood volume causes the problems and thus the logical therapy is to restore blood volume. I do not feel that there is currently much disagreement that the blood volume is reduced in the disease and that the reduction is related to the severity of the disease and thus the maternal and fetal outcome. The real question is does the reduced blood volume cause or is it the result of the disease. Certainly the reduced blood colloid oncotic pressure caused by protein loss and the increased vascular pressure could cause vascular fluid to move to the extravascular space, and it is apparent that the extravascular compartment increases in hypertensive disease of pregnancy. Prospectively, two things have been demonstrated, both by Gant and co-workers[1]: (1) an increase in sensitivity to infused angiotensin II in the patient destined to develop a problem as compared to her counterpart, and (2) an increased clearance of dehydroisoandrosterone sulfate early in pregnancy and a decreasing clearance of DS 3 to 4 weeks prior to the development of symptoms, again using the patient who does not develop hypertensive disease as a control. These investigators have equated DS clearance with placental blood flow, and while there remains some argument that this could be the case, let us assume for the moment it is. We are thus saying that placental flow early in gestation, as a matter of fact up to 3 to 4 weeks before the disease is manifest, is actually greater than normal. To fit this into Dr. Goodlin's concept one might say the increased flow is compensatory for the reduced vascular volume. On the other hand, it could be equated with a hyperexpanded volume early in pregnancy which is reduced only after the disease is manifest.

I would like to insert a word of caution regarding the therapy of expanding the blood volume of a pre-eclamptic patient with serum albumin. I know of one investigator who has found this type therapy associated with congestive heart failure in at least two out of the three cases in which he tried it.

Finally, I would like to ask Dr. Goodlin two questions: (1) explain the severe pre-eclampsia which frequently occurs in the patient with hydatidiform mole who is hyper blood volume expanded; (2) why do his results and Pritchard's differ on the incidence of

thrombocytopenia in severe pre-eclampsia? Pritchard stated it is about 25 per cent; Goodlin feels it is 100 per cent.

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Dr. Lester Hibbard, Los Angeles, California. In our studies of maternal deaths, one of the factors contributing to several of the eclamptic deaths was the fact that a medical consultant called into consultation did not appreciate the pathophysiology of this disease, and as a consequence suggested alternative diagnoses or forms of therapy which were inappropriate and actually harmful.

Dr. Goodlin (Closing). The questions Dr. Quilligan raises are, of course, good ones and I do not have all the answers. I believe that I have only the answer for certain cases of severe pre-eclampsia, those with evidence of reduced blood volume. For the remainder, I shrug my shoulders and treat them with $MgSO_4$ and sedatives.

The women with hydatidiform mole and expanded blood volumes are a worry. I do not know if these women are the ones that develop pre-eclampsia.

Concerning the findings of the Dallas group, I am a strong admirer of Dr. Pritchard, his group, and their studies. But I have noted a 180° shift in some of their conclusions about thrombocytopenia, blood volume, etc., and pre-eclampsia. I obviously do not have the clinical material for study that they have, but do find support for my views in the many European reports. I can only hope that with the accumulation of more data his views will once again swing around to his original concepts. We started off using central venous pressure monitoring in cases of severe pre-eclampsia and it turned into a disaster in two cases. For no matter how often we discussed it, some house officers never got the word that a severe pre-eclamptic has a reduced central venous pressure. In my opinion, if you have a severe pre-eclamptic in whom you have created a "normal" central venous pressure she is on the verge of heart failure. And this is what happened by inappropriate therapy of low CVP pressures.

As regards Dr. Quint's question, increased blood volume means a reduced incidence of pre-eclampsia, and bigger and healthier newborn infants.

We try to speak out against the use of diuretics in pre-eclampsia. Dr. Tom Brewer has made everyone conscious of their deleterious effect and our house staff is very defensive whenever they have been prescribed.

Ectopic pregnancy associated with the intrauterine device: A study of seventy cases

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Seventy cases of ectopic pregnancy associated with an IUD comprised 10 per cent of all ectopics in a 9 year period. This increased to 15 per cent in the last 19 months as more IUD's were in use. In two thirds of the ectopics the IUD had been in situ more than 1 year. Unusual bleeding and cramping attributed to the IUD obscured the diagnosis and resulted in removal or replacement of the IUD in over one half the cases 1 to 8 weeks before surgery. The episodic nature of the abdominal hemorrhage in two thirds of all ectopics resulted in surgery on day 44 average gestational age. The IUD is probably not causal in ectopic pregnancy but does not protect the predisposed patient from ectopic pregnancy which should be suspected in any patient with an IUD who has irregular bleeding and abdominal pain.

THE INTRAUTERINE contraceptive device (IUD) was introduced 50 years ago by Gräfenberg[1] in Germany and Ota[2] in Japan. Both men noted the occurrence of ectopic pregnancy, which we now know is not prevented by any of the currently used IUD's. In the past decade widespread acceptance and use have resulted in an estimated 15 million[3] women throughout the world using this method of birth control in 1974. This is twice as many as in 1969. These women are constantly exposed to ectopic pregnancy, which is a life-threatening surgical condition accounting for 6 per cent of all maternal deaths. Seventy cases of ectopic pregnancy with an IUD have occurred in patients of the Southern California Permanente Medical Group (SCPMG) in the last 9 years. A study of these patients is presented to provide a better understanding of the confusing clinical course and an awareness of the frequency of ectopic pregnancy associated with the IUD.

Materials and results

These 70 cases are part of an ongoing study now numbering 1,428 consecutive ectopic pregnancies up to August, 1975. Table I shows the over-all incidence of ectopic pregnancy in relation to the number of deliveries. A change has occurred since 1966 when the IUD was first used. The number of ectopic pregnancies with an IUD has paralleled the increasing use of the IUD. Lippes loop, Dalkon shield, Safety Coil, and the Copper Seven have been implicated. The total number of IUD insertions and the continuation rate are not available. While the number of ectopic pregnancies has increased, the birth rate has decreased due to the use of more effective contraception, elective sterilization, and abortion on demand. Ten per cent of all ectopics in the last 9 years have been associated with the IUD and in the last 19 months this has increased to 15.46 per cent as more IUD's have been in situ longer (Table I). There was a ratio of 1 ectopic pregnancy with an IUD to 18 uterine pregnancies with an IUD in situ.

The author has personally interviewed most of these 1,428 patients and studied the gross and microscopic material in order to better correlate the symptoms with the findings. These datailed data form the basis for a comparison of ectopic pregnancy with and without an IUD as shown in Table II. It is the same disease in both groups physically and temporarily and follows a consistent predictable pattern. Some differences are noted in Table III due to the selective nature of the IUD group who have elected a method of birth control whereas only 36 per cent of the usual ectopics use any form of birth control. Thirty per cent of all ectopics are infertility patients. There is 35 per cent gross pelvic inflammatory disease (PID) in the usual ectopic group as opposed to only 3 per cent PID in the IUD group. This reflects the proved fertility

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Table I. Ectopic pregnancy and the IUD (increasing incidence of ectopic pregnancy)

1953-1975 (August)		
Births		180,079
Ectopic pregnancies		1,428
incidence	1:126	
1966-1975 (August)		
Births		82,277
Ectopic pregnancies		711
incidence	1:116	
Ectopic pregnancies with IUD		70 (9.85%)
1974-1975 (August) (19 mo.)		
Births		5,252
Ectopic pregnancies		97
Incidence	1:54	
Ectopic pregnancies with IUD		15 (15.46%)
Uterine pregnancies with IUD		258
Incidence (EP:IUD)	1:18	

Table II. Ectopic pregnancy and the IUD (Similarity of 1,428 ectopics and 70 IUD ectopics)

	1,428 ectopics	*70 IUD ectopics*
Average age	30.2 yr.	28.5 yr.
Prior abortion	35%	31.0%
Average days LMP to surgery	56 days	58 days
Surgery—first day of pain	34%	33.0%
Hemoperitoneum over 500 c.c.	52%	53.0%
Location ectopic		
Right tube	52%	51.0%
Left tube	48%	49.0%
Inner one third (cornu)	11%	12.0%
Middle one third (isthmus)	31%	30.0%
Outer one third (ampulla)	58%	58.0%

Table III. Ectopic pregnancy and the IUD (Differences between 1,428 ectopics and 70 IUD ectopics)

	1,428 (%) ectopics	*70 IUD (%) ectopics*
Birth control	36	100
Infertility	31	0
Nulliparous	30	11
PID at surgery	35	3
Sterilized	13	21
Pregnancy not suspected	51	85

Table IV. Ectopic pregnancy and the IUD

	No.	*(%)*
IUD removed for pain and bleeding	28	40
Removed 1 to 16 days before surgery 19		
Removed 21 to 56 days before surgery 9		
IUD changed for symptoms	4	5.7
IUD expelled while pregnant	5	7.1
Preceded by cramps and clots		
Heavy bleeding and clots	10	14.3
Amenorrhea	8	11.43

Table V. Ectopic pregnancy and the IUD

Time IUD in uterus before surgery (Range–7 wk. to 7 yr.)	
Under one year	24
One to two years	22
Two to three years	7
Over three years	17

of the IUD group which is also the reason more of the IUD group elected to be surgically sterilized. In 85 per cent of the IUD group pregnancy was not suspected, the symptoms of ectopic pregnancy being attributed to the IUD as seen in Table IV. Forty per cent of the patients had the IUD removed from 1 to 56 days before the diagnosis was made at surgery. Six per cent had the IUD changed for symptoms and in 7 per cent the IUD was expelled with cramps and clots. Fourteen per cent complained of heavy bleeding and only 11 per cent had amenorrhea. Early heavy bleeding was the main distinguishing feature of the IUD ectopic pregnancy patient.

The time the IUD was in the uterus before surgery ranged from 7 weeks to 7 years as seen in Table V.

It is noteworthy that two thirds of the ectopic pregnancies occurred after the first year of use. The usual side effects of the IUD—intrauterine pregnancy, expulsion, bleeding, and cramping—are far more common in the first year of use of the IUD.

Comment

The IUD eliminates human error in contraception and has no systemic effects. The contraceptive effect persists as long as the device is in place and fertility resumes apparently unaffected when the device is removed. The price paid for these desirable features is a 1 to 3 per cent failure rate and a constant exposure to ectopic pregnancy as well as the common side effects of bleeding and cramping. The IUD often causes increased bleeding and associated cramps as the uterus expels the clots and attempts to expel the device in the first few cycles following insertion. The mechanism of the bleeding as contrasted to endometrial shedding is not known; however, the larger the device, the more the bleeding.[7] In ectopic pregnancy there is usually a precarious implantation with impaired HCG production[4–6] and inadequate hormone support for the endometrium resulting in menstrual-like shedding.[8] This bleeding is exaggerated by the IUD in ectopic pregnancy as noted in Table IV causing bleeding and

clotting near the time of the expected period and persisting when there is inadequate hormone support from implantation. This persistent and often heavy bleeding and cramping beginning in the cycle of conception in ectopic pregnancy was responsible for over half the IUD's being removed, expelled, or changed after which the bleeding usually diminished. Expulsion of the IUD occurs in extrauterine pregnancy, but not in intrauterine pregnancy unless associated with abortion. This is probably due in the former to the increased uterine contractility caused by clots and by decreased progestogen effect both local and systemic.

As the incidence of ectopic pregnancy varies with the incidence of salpingitis, whether specific, postabortal, puerperal, or appendiceal, the incidence of ectopic pregnancy varies geographically and culturally. In Kingston, Jamaica, there is 1 ectopic pregnancy to 28 deliveries[9] but in the United States suburban midwest, it is 1 to 280 deliveries[10]—just one tenth the incidence in Jamaica. Tietze[10] reported 45 ectopic pregnancies in 30,000 IUD insertions in the Cooperative Statistical Program (CSP) of the Population Council. Wie[11] in Taiwan reported 35 ectopics in 38,841 IUD insertions. These studies do not correct for expulsions and removals and the follow-up is short term. It is possible that the incidence is much higher than reported in the CSP and Taiwan studies due to the 50 per cent IUD discontinuation rate in ectopic pregnancy 1 to 8 weeks before the diagnosis is made surgically and because one third of ectopic pregnancies occur more than 2 years after insertion.

Seventy-five per cent of these patients were seen by one or more doctors before surgery without the correct diagnosis being made. This delay in diagnosis due to the IUD is not much greater than the delay in diagnosis in the patients with ectopic pregnancy without an IUD. Both groups come to surgery on the average of 58 and 56 days, respectively, from the first day of the last normal period. The early symptoms of ectopic pregnancy of bleeding and cramping are common gynecologic complaints whereas the inevitable episodic hemoperitoneum occurs later and is a surgical emergency depending on the amount and duration of the bleed. This sudden, sharp, stabbing abdominal pain with nausea, dizziness, and rectal pressure will last 2 hours and disappear unless the bleed continues, in which case the patient presents as an acute surgical emergency as occurs in one third of all ectopic pregnancies with surgery on the day of the first episode of severe pain. Two thirds of the patients have two or more episodes of pain of a progressive nature resulting eventually in surgery.

Whether the IUD is causal in ectopic pregnancy has not been established and is doubtful. It would be dependent on whether the IUD primarily causes salpingitis. The recent reports of midtrimester septic abortions are thought to be the result of the contaminated device being drawn up into the uterus. As of December, 1974, 219 cases of infected pregnancy and 14 maternal deaths were reported to the FDA.[12] It is felt that the PID associated with the IUD in the absence of pregnancy is usually an exacerbation of a pre-existing condition.

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Discussion

DR. JAMES M. MAHARRY, Whittier, California. In reading through the author's accumulated bibliography, it seems that Dr. Hallatt's study of 70 cases of ectopic pregnancy associated with the IUD is the largest series reported. The bibliography contains numerous case reports of what seems to be an actual increase in the number of ovarian pregnancies and abdominal pregnancies associated with the IUD. Did Dr. Hallatt find any ovarian pregnancies?

It would seem that ectopic pregnancy with the IUD has increased 5½ per cent in the past 19 months. Is

this because IUD's are being used more frequently? From Table I of the author's data it would appear that the overall incidence of ectopic pregnancies has doubled, i.e., 1:116 to 1:54.

What has happened to ectopic pregnancies *not* associated with IUD? If we recalculate the author's data using incidence instead of percentages, it would appear that ectopic pregnancy *with* the IUD has increased approximately three times, i.e., 1:1,175 to 1:350. Ectopic pregnancy *without* IUD has doubled in incidence, comparing the arbitrary time periods, i.e., from 1:128 to 1:64.

I surveyed the births and ectopic pregnancies *with* and *without* IUD at Presbyterian Intercommunity Hospital in Whittier, California. Only two ectopic pregnancies associated with IUD's were found. These occurred in 1974. The incidence rate will not change significantly if ectopic pregnancies without IUD's are calculated on this slide. However, it again appears that the overall rate of ectopic pregnancy has doubled, i.e., from 1:320 to 1:153. One wonders if the patients studied in 1953 are the same type of patients studied in 1975. In this 22 year time interval, patients had unbelievable mobility and could spread the social, economic, and sexual changes with great rapidity. One wonders if the patients studied at Kaiser Permanente are the same type of patients studied at Presbyterian Intercommunity Hospital. Some conclusions I have drawn from Dr. Hallatt's paper are: (1) The presence of an IUD provides no protection against ectopic pregnancy, regardless of the number of years of protection it may have provided against an intrauterine pregnancy. (2) The presence of an IUD *delays* and *interferes* with the diagnosis of ectopic pregnancy because both the patient and the physician are misled by signs and symptoms—consequently, their attention is focused on problems with an IUD, rather than the second disease which is the ectopic pregnancy. (3) The increased incidence of ectopic pregnancy associated with an IUD seems relative to the increased use of the IUD, but is this totally true? (4) We are quick to advise patients against sexual intercourse if an inflammatory process exists. We advise the house staff against further pelvic manipulations as it may flare up an existing inflammatory process. We accept "bumper" dyspareunia as a symptom of pelvic inflammation. If the mechanism of contraceptive action of the IUD is from a so-called sterile, inflammatory process, one wonders if the IUD could cause bumper PID or does the IUD cause a different type of endosalphingitis? This is excluding the first 30 days after the IUD has been inserted. If the IUD causes a different type of PID, endosalpingitis, is it mechanical PID, foreign body PID, or old-fashioned (or new-fashioned) and contagious PID? (5) My final conclusion is that the ectopic pregnancy rate reflects the PID rate. Consequently, the real "hooker" is the one with the PID, with or without an IUD.

DR. RICHARD M. SODERSTROM, Seattle, Washington. I would like to tell you about a problem that we have observed at the Mason Clinic in Seattle.

In a recent review of 1,500 laparoscopy sterilizations, we noted a number of cases with chronic, subacute, or acute salpingitis. The technique that we employ is somewhat unique in that we use a wire snare to actually retrieve a specimen very similar to the Pomeroy technique. It is the only technique yet designed in which a generous specimen is removed so that there is no coagulation of the specimen and we can adequately evaluate it histologically. The specimens are usually 1 to 2 cm. and are not coagulated at all.

In reviewing the cases we noted that the patients who had the salpingitis were patients who concomitantly had an IUD in the uterus. I am preempting a paper that will be presented a few weeks from now, but the statistics are as follows: We studied 67 patients with IUD's in the uterus at the time of female sterilization, out of the total of 1,500 sterilizations performed. We compared them in reference to their age, parity, marital status, etc., and found no difference between the two populations. In the population using another form of contraception we found an incidence of chronic, acute, or subacute salpingitis in less than 1 per cent. In the group that had an IUD concomitantly at the time of sterilization, we found an incidence of chronic salpingitis, acute, or subacute in 47 per cent of the cases.

In the last six patients who were wearing IUD's at the time of sterilization, we ground up the tissue and did aerobic and anerobic cultures right at the operating table. As of this date, we have not been able to grow any type of organism. They have all been sterile.

Dr. Daniel Mishell has already shown that the endometrium in IUD wearers develops a sterile endometritis and, therefore, it might be concluded that the endosalpingitis that we are seeing is probably sterile, being chemical-enzymatic in nature. However, it is my feeling that we need to study this further with the idea that possibly this sterile salpingitis does set up a fertile field for some problem of an infectious type that could influence the incidence of ectopics in people who are wearing IUD's.

DR. LESTER T. HIBBARD, Los Angeles, California. I was interested to learn that the incidence of ectopic pregnancy is increasing among Dr. Hallatt's patients. In our hospital the incidence has not changed from a ratio of about 1 to 75 births in the last 20 years.

DR. CHARLES E. WEBER, La Jolla, California. Both Dr. Hallatt and Dr. Maharry have alluded to the fact that there has also been a real increase in the number of ectopic pregnancies in those patients who are not currently using an IUD. I wonder whether or not any of these patients had been previously exposed to an IUD and had developed the sterile endosalpingitis to which Dr. Soderstrom alluded in his discussion?

DR. CLIFFORD C. CHAPPELL, Berkeley, California. I am curious as to whether or not the others have wondered, as I have, whether or not the presumed

increased incidence of ectopic pregnancy is not really a decreased incidence of uterine pregnancy associated with the IUD?

DR. HALLATT (Closing). I want to thank Dr. Maharry for clarifying my statistics showing that the incidence of ectopic pregnancy is essentially the same over the years and is not altered by the changing reproductive pattern.

I do not think that the incidence of ectopic pregnancy is increasing except by virtue of the increase in pelvic inflammatory disease (PID). Certainly Dr. Maharry has documented the sedate, exclusive community of Whittier as being almost free from PID. It must be a lovely place to raise children.

I was fascinated by Dr. Soderstrom's comments. He has certainly had vast experience in tubal sterilization and his conclusion seems to be that the IUD does not cause salpingitis, other than possibly an enzymatic or chemical endosalpingitis. This is the crux of the whole question: Does the IUD cause PID? If it does, then it increases the incidence of ectopic pregnancy and I think the message for us is that PID is actually a contraindication to the use of the intrauterine device. Lee Buxton pointed out very nicely many, many years ago that 22 per cent of all patients who have had a PID will have an ectopic pregnancy if they become pregnant. I have the patient make the decision as to her form of birth control. I do not decide for them. It is their decision and it is very personal. If they want an IUD, I explain that it is not perfect, that there are problems associated with the IUD, and I emphasize that ectopic pregnancy is one of them and it is serious and very difficult to diagnose early. It is very important that we recognize this because 75 per cent of our knowledgeable clinicians missed the diagnosis when given an opportunity to make it, by not recognizing the association of the IUD with an ectopic pregnancy.

Dr. Weber and Dr. Chappell: Your questions were regarding PID as the cause of ectopic pregnancy. I feel that it definitely is and that the IUD is incidental. It does not protect the patient from ectopic pregnancy and the patient is exposed to ectopic pregnancy every month of the year. If they have had a PID, they have a 1 to 5 chance of an ectopic pregnancy if they become pregnant.

We are introducing a few other causes now, such as surgery to open or to close the Fallopian tube. However, PID regardless of its cause is the principal etiology of ectopic pregnancy.

Pituitary tumors in patients with secondary amenorrhea

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This study was undertaken to determine the prevalence of radiologically detectable pituitary tumors among patients seen initially in a gynecology clinic for a complaint of secondary amenorrhea. In a group of 144 women with secondary amenorrhea of more than 6 months' duration, 13 had radiologic abnormalities of the sella turcica detectable with standard skull films without tomography. These gynecologic patients composed more than half of the women in the reproductive age group who were diagnosed at this medical center as having a pituitary tumor. Only one patient with oligomenorrhea or secondary amenorrhea of less than 2 years' duration had a detectable tumor. Thus, for patients with short-term amenorrhea, the risk of having a pituitary tumor is small, especially in the absence of galactorrhea, headache, or changes in vision. However, 12 of 71 patients with amenorrhea longer than 2 years (17 per cent) had detectable tumors and the risk appears to increase progressively with time. Assay of adrenal and thyroid hormones did not discriminate between patients with and without pituitary tumors. Early detection of these tumors is aided by serial sella x-rays, tomograms, prolactin assays, and newer pituitary function tests. Patients presenting with postpill amenorrhea and postpartum amenorrhea illustrate the hazard of interpreting a temporal relationship as a causal one.

THAT WOMEN with pituitary tumors very often have secondary amenorrhea is well known.[1, 2] That women with secondary amenorrhea may have a pituitary tumor is also well known, but how often this happens is not. The answer to this question is important to gynecologists and to others who treat women for amenorrhea. Since an x-ray examination of the sella turcica has been obtained regularly on patients with secondary amenorrhea seen in our Reproductive Endocrinology-Infertility Clinic, we were able to determine the prevalence of radiologically detectable pituitary tumors among these patients.

To determine which clinical or laboratory findings had been useful in the early detection of pituitary tumors, we have reviewed the records of three groups of patients: gynecologic patients with a radiologically detectable pituitary tumor, nongynecologic patients with a pituitary tumor, and gynecologic patients with long-term amenorrhea but no tumor demonstrated by sella x-rays. More than half the women in the reproductive age group who have been treated for pituitary tumor in our medical center over the last 11 years had been seen initially in the gynecology clinic.

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Material and methods

Between 1963 and 1973, 448 women in the reproductive age group, 15 to 45 years, registered in the Reproductive Endocrinology-Infertility Clinic of the Department of Gynecology and Obstetrics with the complaint of oligomenorrhea or secondary amenorrhea. Of these, 304 had oligomenorrhea, defined by the occurrence of at least one spontaneous bleeding episode during the 6 months preceding registration. These patients are included in Fig. 3 but not in subsequent figures or tables. For this study we defined the duration of secondary amenorrhea of the remaining 144 patients as the total time since the last spontaneous menses including any time during which drugs, such as oral contraceptives, which induce uterine bleeding were used. Since many patients were referred to this clinic for therapy with ovulation-stimulating drugs, the proportion of patients with long-term amenorrhea may be greater than would be seen in an unselected gynecologic practice.

Twenty-one patients seen in this clinic had abnormal sella x-rays and had pituitary tumors diagnosed in the

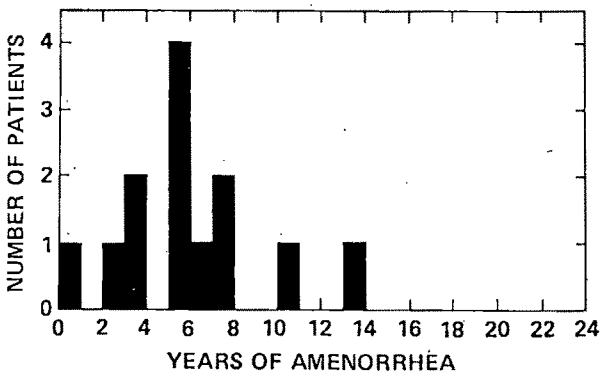


Fig. 1. Duration of amenorrhea for 13 women registered in the gynecology clinic who were found to have abnormal sella x-rays.

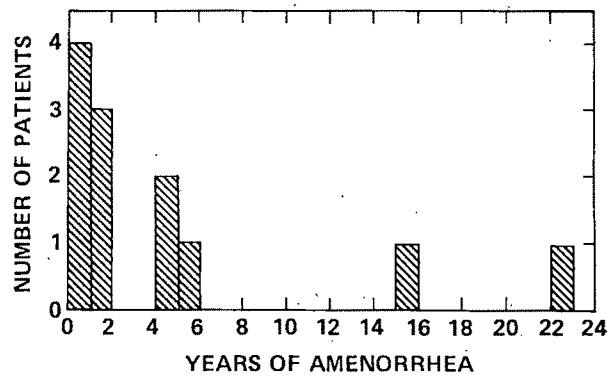


Fig. 2. Duration of amenorrhea for 12 women from other specialty clinics with abnormal sella x-rays.

Table I. Frequency of abnormal sella x-rays and duration of amenorrhea

Years amenorrhea	*No.*	*Abnormal sella*	*Per cent*
½ to 1	38	1	3
1 to 2	35	0	0
2 to 5	36	3	8
>5	35	9	25
Total	144	13	9

Reproductive Endocrinology Clinic. Five of these women were excluded from this study because they did not have secondary amenorrhea (two had primary amenorrhea, one was pregnant, and two had had a hysterectomy). Three other patients were excluded because they had been treated for a pituitary tumor prior to being seen in this clinic. The records of the remaining 13 patients with secondary amenorrhea and enlargement of the sella were reviewed in detail.

During the same decade, 32 other women had a pituitary tumor diagnosed initially in other clinics of the Medical Center—Neurosurgery, Endocrinology, or Radiotherapy. Only 14 were in the age group 15 to 45 and two of these were not at risk of secondary amenorrhea, one having had a hysterectomy and other having primary amenorrhea. The records of the remaining 12 were reviewed in detail.

Plasma concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyrotropin (TSH), growth hormone (GH), testosterone cortisol, and thyroxin (T_4), were measured with radioimmunoassay or competitive protein-binding assays.[3–8] Urinary gonadotropins were measured by bioassay.[9] Stimulation and suppression tests with metyrapone, dexamethasone, water, insulin (insulin tolerance test, ITT) or thyrotropin-releasing hormone (TRH) were done by standard methods.[4, 10, 11]

Results

The duration of amenorrhea for patients with pituitary tumors was longer among those who were seen initially in the gynecology clinic (Fig. 1) than among those seen in other clinics (Fig. 2). Only one of the 13 patients (7 per cent) seen in the gynecology clinic had amenorrhea of less than 2 years' duration. However, seven of the 12 patients (58 per cent) seen initially in the neurosurgery, endocrinology, radiotherapy clinics had amenorrhea of less than 2 years' duration, four having bled spontaneously during the preceding year. In the combined group of 25 patients at risk of menstrual disturbance, 20 (80 per cent) had amenorrhea of at least 1 year.

Only 144 (32 per cent) of the 448 women presenting for gynecologic consultation because of oligomenorrhea or amenorrhea had not bled spontaneously during the past 6 months and only 71 had amenorrhea persisting for more than 2 years. It is in this latter group, however, that we found 12 of the 13 patients with abnormal sella turcica films (Fig. 3). Of all patients with amenorrhea of greater than 5 years' duration, the nine patients with abnormal x-rays represent 25 per cent. Thus, because of decreasing numbers at risk and increasing numbers found to have abnormal x-rays, the prevalence of an abnormal sella (pituitary tumor) among patients seen initially for gynecologic consultation was increased dramatically with duration of amenorrhea (Table I).

Most patients had other symptoms suggesting pituitary disease. The symptoms other than amenorrhea differed among the three groups of patients (Fig. 4). Among the gynecologic patients with tumor, only one

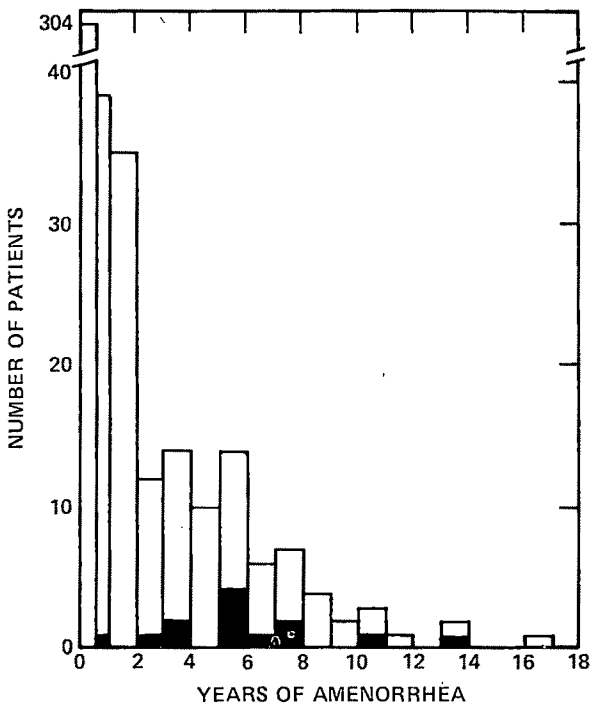


Fig. 3. Duration of amenorrhea for 448 women registered in the gynecology clinic with a complaint of oligomenorrhea or amenorrhea. Solid bars identify the 13 women with pituitary tumors diagnosed by x-ray examination.

had no symptoms other than amenorrhea. Galactorrhea was noted by seven of the 13 (53 per cent)—a striking difference from the other groups. A number had a change in habitus (usually weight gain), persisting headaches, or visual disturbance. Even more of the patients seen initially in other clinics had habitus changes (including one with acromegaly and two with Cushing's syndrome), headaches, and visual disturbances.

All 13 of the gynecologic patients had an abnormal sella turcica on standard films. Tomograms further defined the presence of double floor, unilateral depression of the floor, enlargement, and/or erosion. Pneumoencephalography and/or anteriography have been done in most patients prior to treatment (Table II). Five patients had visual field defects and in three extrasellar extension of the tumor was demonstrated by pneumoencephalography or arteriography; the others had only slightly abnormal visual fields. One other patient (case 5) with normal visual fields had suprasellar extension demonstrated by arteriogram.

Of the patients who have completed the diagnostic studies to date, nine have had radiation therapy, usually 5,000 rads to the pituitary via rotational therapy with the linear accelerator,[12] and six have had surgery.

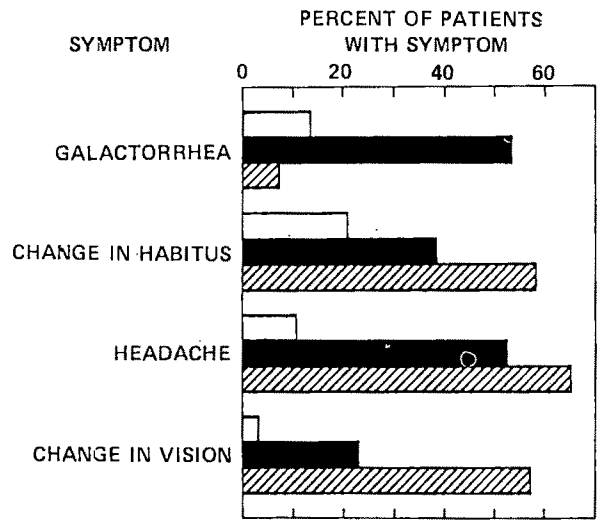


Fig. 4. Prevalence of endocrinologic and neurologic symptoms. Open bars, 59 gynecologic clinic patients with normal sella x-rays and amenorrhea greater than 2 years. Solid bars, 13 gynecology clinic patients with abnormal sella x-rays. Hatched bars 12 patients initially seen in other clinics with abnormal sella x-rays.

Two of the operations were for acute visual symptoms requiring decompression following radiation therapy. At the request of her parents, one mentally retarded patient (case 1) with no evidence of extrasellar extension did not receive therapy. Two are under continuing study and one has been lost to follow-up.

Hormone measurements used to evaluate the 13 gynecologic patients with sellar enlargement are listed in Table III. Plasma LH and FSH were normal in several cases and total urinary gonadotropins were detectable in six of the cases studied before treatment. Adrenal and thyroid function as tested by standard methods were normal in most cases. Metyrapone stimulation and dexamethasone suppression tests of ACTH response were normal in the several cases tested.

Comment

The findings of this study support several conclusions reached by authors of previous retrospective studies of patients with pituitary tumors. Downing, Engel, and Betz[1] reviewed 248 reports in the neurosurgical and gynecologic literature of women under 45 years of age who had pituitary tumor and added 26 cases of their own. The great majority (92 per cent) had menstrual abnormalities.

The present study provides data to answer a question of interest to the gynecologist or endocrinologist: "What is the risk to a patient with secondary

Table II. History, tests, treatment, and status of 13 gynecologic patients with abnormal sella turcica x-rays

Case No.	Year of diagnosis	Age	Parity	Amenorrhea (yr.)	History	Response to			Evidence of extrasellar extension		
						Progesterone	Clomid	Pergonal + HCG	Pneumogram	Arteriogram	Visu field
1	1968	26	0	0.5	50 lb. weight loss, irritability				–	–	–
2	1973	30	1	2	Headaches; ovarian wedge resection age 28	No	No	Yes		+	+
3	1968	30	0	3	Virilization (congenital adrenal hyperplasia); headaches; hyperpigmentation (Nelson's syndrome)				–	–	+
4	1973	20	0	5	Galactorrhea				–	–	–
5	1969	22	0	5	Headaches, galactorrhea	Yes			–	+	–
6	1973	25	2	5	Postpartum onset; headaches galactorrhea, weight gain; ↓ libido, husky voice (acromegaly)	No			–		–
7	1973	28	0	6	Amenorrhea after 1 yr. oral contraceptive use	No	No		–	–	–
8	1972	31	2	7	Amenorrhea after 5 yr. oral contraceptive use; headaches, galactorrhea, increased sweating (acromegaly)				–		–
9	1972	25	0	10	Amenorrhea after 5 yr. oral contraceptive use; headaches, decreased secondary hair				+	+	+
10	1964	33	0	13	Wedge resection age 26; recent development of blind spot				+		+
11	1972	26	1	3.5	Postpartum onset; galactorrhea	Yes	Yes		–		+
12	1967	21	0	5	Amenorrhea after 4 yr. oral contraceptives; galactorrhea	No					–
13	1964	30	0	7	Galactorrhea	No	No	Yes			–

amenorrhea of having a pituitary tumor detectable by standard sella films at the time of her initial consultation?" The risk for patients with amenorrhea of less than 2 years' duration who have no other symptoms suggesting a pituitary disorder seems to be quite low. Only one of 377 patients who presented to our clinic with amenorrhea of 6 to 24 months had radiologic evidence of pituitary tumor. However, our policy has been to obtain the following baseline studies—visual field determination, x-ray of the sella turcica and, recently, a determination of serum prolactin on all patients with amenorrhea of over 6 months' duration and to repeat the x-ray annually if the amenorrhea persists.

Patients with pituitary tumors who consult a gynecologist for prolonged amenorrhea probably have tumors that are slow growing. Because of the slow growth, x-rays of the sella turcica repeated annually may show subtle changes. Serial x-rays were of value in the diagnosis of several patients (cases 3, 4, 5, 6, 7, and 11) reported here. On the other hand, patients with pituitary tumors who consult other specialists with complaints of headache or visual disturbances often have tumors that are faster growing and thus have earlier suprasellar extension. These patients may also have amenorrhea or habitus changes (especially those associated with acromegaly or Cushing's syndrome) which lead them to seek early consultation.

The risk to the patients with secondary amenorrhea increases dramatically with the duration of amenorrhea. Twelve of the 71 patients with amenorrhea of over 2 years' duration and nine of the

Therapy		
Radiation	Surgery (histology)	Current status
		No change sella. Occasional spontaneous uterine bleeding
+	(Necrotic)	Vision normal. No hormone replacement. Ovulated spontaneously
+	(Chromophobe)	Died after neurosurgical therapy at another hospital
+		Amenorrhea and galactorrhea persist
+		Estrogen replacement
+	(Acidophilic)	No galactorrhea; adrenal replacement
+	(Necrotic)	Developed galactorrhea postoperatively
+		Amenorrhea persists; no hormone replacement
+	(Chromophobe)	Adrenal, thyroid, estrogen replacement
+	(Chromophobe)	Amenorrhea persists; no hormonal replacement
+		Undergoing treatment
		Lost to follow-up
		Sella enlarging; undergoing evaluation before treatment

35 patients with amenorrhea of over 5 years' duration had pituitary tumors. Patients with long-term amenorrhea thus form a group with a high risk of pituitary tumors.

In another high-risk group are those with amenorrhea and galactorrhea. Over 25 per cent of these patients have a pituitary tumor.[1, 2, 14, 15] In this series, seven of the 13 gynecologic patients with galactorrhea and long-term amenorrhea had tumors (53 per cent). Other symptoms such as changes in habitus (weight), headaches, or changes in vision, which the patient may or may not perceive as worrisome, may also suggest the presence of a pituitary tumor.

The data in Table II illustrate the hazard of interpreting a temporal relationship as a causal one or a syndrome as a diagnosis. Pituitary tumors were found in patients with postpill amenorrhea (cases 7, 8, 9, and 12), those with postpartum amenorrhea (cases 6 and 11), and in patients who had previously had wedge resection of the ovaries for chronic anovulation (cases 2 and 10).

Patients 5 and 11, who later had enlargement of the sella, bled after the injection of progesterone given as a test of estrogen status repeatedly 1 and 2 years before the diagnosis was made. We may assume that they had small pituitary tumors which at that time had not caused estrogen deficiency. One patient conceived after clomiphene citrate therapy (Clomid, Richardson-Merrill) and one after exogenous gonadotropin therapy. Another patient ovulated but did not conceive after gonadotropin therapy.

Prolactin assay promises to be useful in the early detection of pituitary tumors even in patients without galactorrhea.[4, 7, 11, 14] Assay of the concentration of other pituitary, adrenal, and thyroid hormones is necessary before treatment but these assays were not particularly useful in determining whether a patient in this series did or did not have a pituitary tumor as the cause of her secondary amenorrhea.

Further clinical studies are needed to assess the value of modern pituitary function tests in the early detection of pituitary tumors.[3, 10, 11, 16, 17] The response of GH, PRL, and cortisol or ACTH to insulin-induced hypoglycemia, the response of FSH and LH to gonadotropin-releasing hormone (Gn-RH, L-RH), and the response of TSH and PRL to thyrotropin-releasing hormone (T-RH) is abnormal in many patients with a variety of pituitary disorders including tumors. At present few results of tests of women with untreated intrasellar pituitary adenomas have been reported. Moreover, a significant proportion of patients with functional amenorrhea also have abnormal responses and many patients with small intrasellar microadenomas, and even some patients with suprasellar tumors or with tumors previously treated with surgery and/or radiation, have normal responses. The combination of a subnormal response of GH to hypoglycemia and hyperprolactinemia is quite suggestive of pituitary tumor.

The discriminatory value of any one or a combination of these costly pituitary function tests will, of course, be improved if used to screen a high-risk group. Amenorrhea of 3 months or longer occurs each year in about 3 per cent of women at risk but amenorrhea of a year or longer is much less common (Fig. 3).[18] We plan to use these tests along with tomography of the sella and visual field determinations for patients with amenorrhea persisting for 2 years or associated with galactorrhea. We plan to repeat tomog-

Table III. Hormonal studies of 13 gynecologic patients with abnormal sella turcica x-rays

	Pituitary						
	Gonadotropins			*Prolactin*		*Growth hormone*	
	Urinary	*FSH*	*LH*	*Baseline*	*After TRH*	*Baseline*	*After insulin*
Normal range (follicular phase)	*6-48 (M.U.U./day)*	*3-25 (mI.U./ml.)*	*4-25 (mI.U./ml.)*	*<40 (ng./ml.)*	*50-200% above baseline (ng./ml.)*	*<7 (ng./ml.)*	*>10 (ng./ml.)*
1	6-48*	10	11	11.4			
2	6-48	14†	21†	9.0†		0.5	3.7
3	21						
4	<13	12.8*	17.7*	210*	No change	0.6	20
				170†			
5	<3	<1.5†	8.0†	81†			
6	<8	3.0	5.0	21		497	
						30†	
7	<6			505		1.7	15
		3.8†	5.0†	236†	304†		
8	6-48					90	
		6.5†	3.0†			12*†	
9	<3						
10	<6	9.0†	8.0†	194†			
11	<3	5.0	3.5	75		20	100
12	6-48						
13	6-48	9.0	8.0				

*Mean of 2-5 values.
†After treatment.

raphy of the sella at yearly intervals for those who do not resume cyclic menses or conceive. For patients with initially normal examinations, repeated visual field determinations may not be needed in the absence of radiologic change in the sella. The value of repeated pituitary function testing needs to be defined.

Patients with intrasellar tumors for whom amenorrhea may be the only symptom can now be identified but there is no general agreement on the best approach to treatment—none, radiation, surgery, or both. The transphenoidal approach to the sella which recently has reassumed an important place in neurosurgery may allow removal of small tumors without destruction of the normal anterior pituitary or pituitary stalk and result in return of normal cyclic endocrine function in some cases.

On the other hand, there is general agreement that patients with suprasellar extension must be treated to prevent the occurrence of progression of visual and neurologic symptoms. Patients with abnormal sella x-rays, even those with normal visual fields, should have a pneumoencephalogram and a cerebral arteriogram to detect suprasellar extension and to identify those with other causes for radiologic changes of the sella such as aneurysm or the empty sella syndrome.[19, 20] The place of the computed tomographic brain scan in the detection of suprasellar extension is not yet fully established.[21]

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Ovary	*Adrenal*		*Thyroid*
Karyo-pyknotic index	*17OHCS*	*17KS*	*T_4 (PBI)*
5-40 (%)	*4-10 (mg./day)*	*5-18 (mg./day)*	*2.9-7.5 (4-8) (μg/dl.)*
5	12.0*	10.8*	5.2*
10	3.4	10.1	3.2
	0.5	47	(8.2)
0*	12.5*	21.5*	4.5
0*	4.4*	6.3*	6.6*
2*	10.0*	15.9*	7.4*
6		18.6*	5.2*
	30†		
1	10.2	8.9	3.5
	6.0	1.5	2.5
	7.3	10.8	(5.0)
2*	11.7	9.8	3.7*
1	5.3	16.7	(7.0)
3*	8.9*	17.5*	4.5*

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Discussion

Dr. William J. Dignam, Los Angeles, California. Dr. Lamb has presented a most interesting review of his experience with patients with amenorrhea and pituitary tumors. It is enlightening to hear of the course of these patients over significant periods of time since many of us have the opportunity to see such patients only occasionally and, even then, for just a visit or two. It is only from long-term, carefully documented observations, such as those presented today, that we can gain a correct impression of the course of these illnesses.

We have been told that pituitary tumors are particularly common in women with long-standing amenorrhea and it has been emphasized that these tumors develop slowly over a period of years whereas more rapidly growing tumors may have earlier suprasellar extension and are more likely to be manifested by headaches and visual disturbances. Patients have been presented to illustrate possibly distracting features such as the occurrence of the amenorrhea in the postpartum period or after a period of the use of contraceptive pills. Two patients had had a wedge resection of the ovaries. Two patients had had withdrawal bleeding following the administration of progesterone at a time when a small pituitary tumor was probably present. These are all points well worth remembering in order that we may remain ever vigilant to suspect and search for pituitary tumors.

These tumors are not malignant in the sense of metastasizing, but they may be particularly threatening if they extend to the area of the optic chiasm and endanger the patient's vision, especially if an acute enlargement of the tumor occurs, as with hemorrhage. In addition, they may severely compromise the endocrine function of the pituitary or some of the important areas in the hypothalamus such as the satiety center. It, therefore, behooves us to find them when they are small and have caused little damage.

Some of these tumors are endocrinologically active and produce hormones such as prolactin, or growth hormone, or adrenocorticotropic hormone, which help us in the detection of these tumors. Others, however, do not produce hormones but produce amenorrhea by inhibition of gonadotropin production. We take some solace if the responsible lesion is in the hypothalamus since such problems are much less likely to be due to tumor. The direct measurement of releasing hormones in the peripheral circulation will be of major assistance in this delineation, when those measurements are generally available. At the moment such is not the case so that a variety of functional tests have been described. One such test was presented to this society in 1973.[1] Those authors employed the infusion of arginine, LRF, and TRF. At our institution we feel that growth hormone and prolactin measurements are among the most sensitive indices of altered pituitary function but find that it is difficult to assess diminished function from baseline levels of growth hormone. We, therefore, tend to employ propranolol and levodopa and note their effect on these levels. This has been a simple, practical, and informative test. Dr. Lamb favors the use of imsulin-induced hypoglycemia and the response of prolactin to water loading.

I should like to ask Dr. Lamb a few questions. In patients with long-standing amenorrhea and normal sella turcica films, are his specific diagnostic tests those indicated in the paper? He has listed urinary gonadotropins, plasma, follicle-stimulating hormone, luteinizing hormone, prolactin, thyrotropin, growth hormone, testosterone, cortisol, and thyroxine. If all of these are normal, are any stimulation or suppression tests performed? If not, what *are* his indications for stimulation or suppression tests and which tests does he now favor?

He has indicated that the risk of tumor is significantly elevated in patients with both amenorrhea and galactorrhea. What further tests are performed for patients with elevated prolactin levels? Does he feel that prolactin-secreting adenomas of the pituitary are true neoplasms? How are they identified and should they be removed if the sella is not enlarged?

In at least one of the patients a change in the sella was discovered by an increase in the volume. Does this measurement offer an advantage not obtainable from tomograms?

He has indicated that the place of the EMI scanner in detecting suprasellar extensions was not yet established but this is a rapidly changing area. Have there been any recent developments to modify that opinion?

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DR. ROBERT B. JAFFE, San Francisco, California. I should like to emphasize the implicit message in both Dr. Lamb's and Dr. Dignam's comments, namely, that we should not be complacent about individuals who present with amenorrhea as, particularly when the amenorrhea is associated with either galactorrhea or hyperprolactenemia, the incidence of neoplasm is not infrequent.

Since February, 1974, I have seen 25 patients with pituitary neoplasms. The bulk of these have been microadenomas. Some of these microadenomas would not be recognized by simple sellar x-rays, and were only picked up with sella tomograms. We have found that the utilization of the gonadotropin-releasing hormone will, in many instances, distinguish between microadenomas and the large pituitary neoplasms. We find that in patients with idiopathic galactorrhea, similar to those with microadenomas there is an exaggerated response of the gonadotropins to the gonadotropin-releasing hormone; whereas in those individuls with large neoplasms, at least those greater than 1 cm., the response of both LH and FSH to the gonadotropin-releasing hormone is markedly blunted when compared with that of normal individuals. We would suggest that in all individuals in whom there is galactorrhea and amenorrhea, or even in those individuals who have amenorrhea and hyperprolactenemia, even without observable galactorrhea, sella x-rays combined with studies of the various releasing factors and other agents which assess pituitary function are advantageous. In collaboration with our neurosurgeon, Dr. Wilson, we have found that very good results can be obtained by shelling out the microadenoma, leaving the bulk of normal pituitary tissue behind. And the majority of patients thus treated have had resumption of menses and decrease or elimination of their galactorrhea. One note of caution: Not all enlarged sella turcicas are due to pituitary tumors. We had one patient, whom we will report shortly, who had a markedly enlarged sella with suprasellar extension of a suspected neoplasm. She had sexual infantilism, primary amenorrhea, and the diagnosis made both radiologically and by the neurosurgeon of a pituitary neoplasm with suprasellar extension. However, when we measured her pituitary hormones, we found that both her TSH and prolactin were markedly elevated. We therefore made the diagnosis in this adult, similar to the diagnosis that Drs. Grumbach and Van Wyck have made in children, of primary hypothyroidism with secondary compensatory pituitary hypertrophy. Treating that woman with thyroxin, rather than surgically, menses began, secondary sexual characteristics manifested themselves, and we eventually, delivered her of a term pregnancy without complications.

DR. ROBERT A. SACK, Whittier, California. To document the fact that these tumors occur in other species I

would like to present a brief case report. The patient, a 20-year-old thoroughbred mare, had been infertile for 4 years—in horse parlance, a "barren mare." In the spring of this year, as the first slide reveals, she began to exhibit a marked increase in body hair. Shortly thereafter it was noted that she was drinking 50 to 60 gallons of water per day, while urinating almost constantly. Because of increasing muscle wasting she was humanely destroyed. At autopsy, as the second slide demonstrates, there was a pituitary tumor. The third slide reveals it to be a chromophobe adenoma.

DR. LAMB (Closing). In answer to Dr. Dignam's first two questions: For patients with normal sella turcica films and amenorrhea of over 2 years' duration or other symptoms such as galactorrhea suggesting a high risk of pituitary adenoma, we now order anterior and lateral tomograms of the sella, a formal visual field examination, a serum prolactin, FSH, LH, cortisol, and T_4; we no longer use urinary assays for gonadotropins or steroids. The sella tomograms must be interpreted with caution because the subtle changes suggestive in pituitary tumors are also seen in the films of many patients with no pituitary disease.[1] As a minimum follow-up, we suggest an annual lateral sella film and clinical examination. These studies should identify patients such as those we have presented today with tumors of sufficient bulk to change the sella turcia. If we are to detect microadenomas rather than gross tumors, we will need pituitary function studies such as those using insulin, gonadotropin-releasing hormone, and TRH given alone or together. Based on a still-limited number of reports of such studies in women of the reproductive age with untreated intrasellar tumors, it appears that changes in serum concentration of PRL, LH, and GH are the most sensitive indicators of disordered pituitary function and that adrenal and thyroid functions are preserved in most of these patients. Hopefully, such studies will yield a clinically practical method to differentiate patients with small pituitary tumors from those without. At present, a combination of an elevated serum prolactin, a blunted response of GH to insulin, and changes in the anterior and lateral sellar tomograms is very suggestive of pituitary tumor.

Dr. Dignam's third question relating to the testing and management of patients with elevated prolactin levels is an important question for which a satisfactory answer is not yet available. The response to stimuli affecting the hypothalamus by some patients with gross prolactin-producing adenomas suggests that disordered hypothalamic function could result in hyperplasia of the prolactin-secreting pituitary cells. This localized overgrowth would then be no more a true neoplasm than the adrenal hyperplasia which results from excessive ACTH stimulation or the enlarged pituitary in the patient Dr. Jaffe mentioned. We must also remember that among patients without endocrine symptoms who came to autopsy, the incidence of intrasellar pituitary tumors is not insignificant; various figures in the range of 10 per cent have been cited. Perhaps, as we come to apply our knowledge of the controls of prolactin secretion, we will find that medical therapy may be used safety in treating patients with prolactin-secreting microadenomas. However, at present we have to balance the risks of radiation therapy or transphenoidal hypophysectomy against the benefits of early treatment which may prevent impairment of vision and may improve endocrine and reproductive function.

In response to the fourth question: The diagnosis of pituitary tumor may be suspected before the sella is enlarged beyond the accepted bounds by detecting progressive changes in the sella or an increase in volume by serial standard films or by tomography. We have cited several cases in which annual skull films showed a progressive change in the borders or an increase in volume of the sella.

Finally, although experience in the use of the EMI scan to detect suprasellar extension is increasing rapidly, our radiologists and neurosurgeons currently feel that a pretreatment pneumoencephalogram and cerebral arteriogram are necessary in most cases to rule out other causes of parasellar changes such as an aneurysm and a tumor other than a pituitary adenoma. The computed scan is not useful in detecting intrasellar lesions.

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Prolapse of the vaginal vault

Improved techniques for management of the abdominal approach or vaginal approach

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A brief discussion of the history of techniques for the surgical management of prolapse of the vaginal vault is presented. The author's method for the abdominal procedure, sacral colpopexy, is presented together with a summary of twelve patients in whom it was used. The author's modification of the technique of the vaginal operation, "the anterior approach," is presented because it appears to make resection of the enterocele sac and identification of uterosacral ligaments easier and their utilization more effective.

THE OPERATIVE treatment of prolapse of the vaginal vault is a major challenge to the gynecologist's surgical skill, particularly when preservation of coital function is sought—as it often is even for women of advanced years.

Support of a prolapse with a carefully fitted plastic vaginal pessary may occasionally be preferable to surgery. The patient for whom operation is contraindicated by concurrent medical problems and for whom coital ability is unimportant may thus be offered great relief of symptoms without surgical risk. Whenever possible, however, operative correction is the preferable mode of therapy.

Both the partial and the complete colpocleisis procedures are used only rarely today. In three San Diego hospitals (Mercy, Sharp, and University), with gynecologic services busy enough to accomplish over 2,000 hysterectomies annually, there were only two LeFort operations during the two years 1973-74. Colpocleises have become almost historical procedures because of the availability of other techniques that avoid their failure rates, the frequent postoperative urinary incontinence, and loss of sexual function.

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The incidence of prolapse of the vaginal vault is difficult to ascertain. Many patients tolerate it uncomplainingly. Occasionally a patient has been seen who has resigned herself to complete eversion of the vagina (sometimes reducing it for coital purposes), often she presents herself for some completely different complaint.

A review of the gynecologic operations performed in the above three hospitals over a 2 year period revealed 13 abdominal colpopexies. In a 1 year period there were 98 repairs of cystocele and rectocele for patients who had had prior hysterectomy, only 11 of the 98 were vaginal hysterectomies. In 60 per cent of these patients the primary complaint was that of urinary stress incontinence. There seems little doubt that some of these patients had partial prolapse of the vaginal vault; yet the operative notes rarely made any mention of it, of enterocele, or of utilization of the uterosacral ligaments in the repair.

Recent years have seen a marked increase in the numbers of both abdominal and vaginal hysterectomies—and the operations are being performed on considerably younger women than was the case a generation or two ago. One suspects that when these women reach the age at which their mothers and grandmothers developed uterine prolapse, many of them will develop prolapse of the vaginal vault. It is doubtful that improved obstetric care or the more frequent use of cesarean section will entirely avert this anticipated greater incidence of vault prolapse.

Protrusion from the introitus is the most frequent

complaint to which prolapse of the vaginal vault gives rise, but pelvic pain, pressure, or bearing-down symptoms are not infrequent. Dyspareunia is rare, as is urinary incontinence. On occasion, the patient denies any symptoms, and the prolapse is found upon routine examination.

The causes of vaginal vault prolapse remain obscure. Damage to pelvic structures during labor and delivery is often blamed, or the gynecologic surgeon is accused of inadequate attention to supporting structures during the performance of hysterectomy. Nichols[1] has said, however, that "many postoperative enteroceles are in fact extensions of an unrecognized and therefore untreated process already in progress at the time of the original operation." Clearly, obstetric and surgical factors are of etiologic importance and every effort should be made to avoid them. Nevertheless, uterine prolapse occasionally occurs in virgins, in nulliparous women, or in women whose deliveries have all been by cesarean section. Moreover, in contrast, many a woman with a deeply lacerated perineum, gaping introitus, and history of the vaginal birth of large babies maintains excellent vaginal vault support throughout life. The importance of inherent weakness of supporting tissues and postmenopause tissue atrophy as major causative factors is inescapable. Doubtless the role played by these factors is often overlooked and the blame for vault prolapse unfairly attibuted to a previous surgeon.

Surgical procedures

Frankel's[2] statement in 1927 that "an operation based on sound principles good for all cases is still wanting" remains valid today. Moreover, the decision on whether to use an abdominal or vaginal approach, or both, is not always easy to make. It is our practice to employ the abdominal operation for patients with a vagina of normal caliber, but to use the vaginal procedure when the vagina is abnormally enlarged so that a cystocele or rectocele (and the inevitable enterocele) accompanies the prolapse. If the abdominal technique employs any type of synthetic, nonabsorbable mesh, it seems undesirable to combine it with any vaginal procedure and thus bring about risk of chronic infection and the necessity for eventual removal of the foreign material.

A variety of techniques for the abdominal operation has been reported. Many authors have recommended the use of strips dissected from the anterior sheath of the rectus abdominis muscle. Shaw[3] (Fourteenth president of the Pacific Coast Obstetrical and Gynecological Society) presented his method in his presidential address in 1948; and Guiou[4] presented his method;

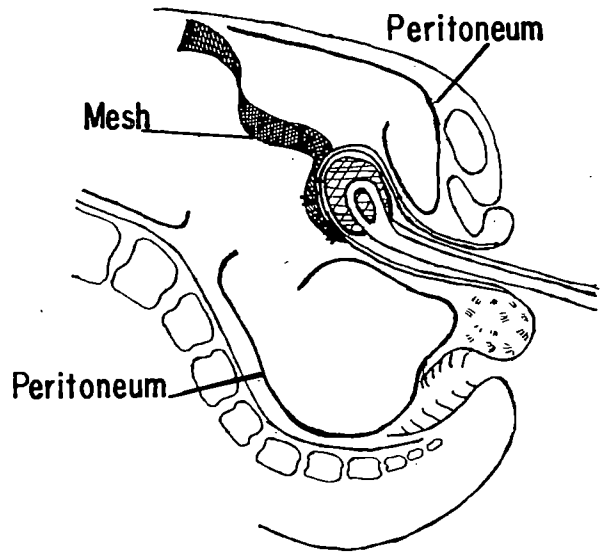


Fig. 1. Vaginal apex elevated, Mersilene mesh sutured to vagina previously denuded of peritoneum.

Fletcher[5] crossed strips of this fascia behind the bladder and sutured the vaginal vault to their posterior aspect; Ward[6] used ox fascia in a similar fashion. These were essentially efforts to replace attenuated round ligaments. Mengert,[7] by means of an interesting study on several cadavers in 1936, demonstrated the worthlessness of the round ligaments as supporting structures: over a pulley he attached a weight to a tenaculum on the cervix; then by successively dividing the various structures attached to the uterus he showed that the round ligaments did not contribute any significant supportive strength. Frankel[2] in 1927 sutured the vagina to the anterior abdominal wall, even with the uterus still present. In 1965 Langmade[8] reported an original and ingenious operation utilizing Cooper's ligaments. These are considerably stronger than any fascial strips, and their use comes close anatomically to constructing new cardinal ligaments.

All of these operations, however, tend to pull the vaginal vault forward (least of all the Cooper's ligament operation) predisposing the cul-de-sac to enterocele formation. Arthure and Savage,[9] recognizing the likelihood of later enterocele development, sutured the prolapsed uterus to the sacrum in an effort to obliterate the cul-de-sac, but sutured the prolapsed vault to the anterior abdominal wall. Friedman and Meltzer[10] used reconstituted collagen mesh for augmentation of the endopelvic fascia, wrapping the vaginal vault and reinforcing the uterosacral, cardinal, and round ligaments. Lane[11] was the first to use braided synthetic material as a supporting structure for the vault, and similar reports by Richardson and

Table I. Sacral colpopexy

Patient	*Age*	*Wt. (lbs.)*	*Parity, largest birth*	*Previous gyn. surgery*	*Date of colpopexy*	*Follow-up at last visit (mo.)*
1.G. M.	53	154	Para 1 Wt. 7-8	1950 V.H., 1960 rep. cysto. and recto. and abd. susp. to rd. lig., 1970 M.M.K. + rep. recto. and entero	12-8-71	42
2.C. C.	62	122	Para 2 Wt. 6	1956 V.H. + rep., 6 mo. later—vag. rep., 1966 M.M.K., 1970-Fletcher crossed suspender + Moschcowitz, 1971 rep. recto. + entero.	3-22-72	38
3.R. K.	72	142	Para 3 Wt. 9-14	1961 bladder rep., 1971 M.M.K., few months later V.H. for prolapse, 2 months later repeat M.M.K.	10-25-72	32
4.P. S.	60	153	Para 2 Wt. 8-2	1957 V.H., 1972 M.M.K.	11-14-72	23
5.E. P.	62	138	Para 1 Wt. 7-14	1961 T.A.H. + B.S.O., 1972 rep. cysto., recto., and entero.	4-20-73	26
6.M. S.	56	114	Para 2 Wt. 5+	1968 T.A.H. + vag. rep.	5-8-73	27
7.M. W.	71	183	Para 1 Wt. 8-8	1939 supracervical hyst., 1955 vag. excision CVX. + rep. cysto. and recto.	8-28-73	22
8.G. B.	72	156	Para 1 Wt. 6-6	1942 V.H., 1972 rep. cysto. and recto.	9-17-73	24
9.L. R.	55	155	Para 1 Wt. 7-14	1972 V.H., 1973 M.M.K., 4 months later rep. recto. + entero.	1-15-74	17
10.D. E.	64	189	Para 2 Wt. 8-10	1934 uterine susp., 1972 T.A.H. + B.S.O., 1972 ant. rep. for stress incont., 1973 M.M.K.	3-25-74	15
11.E. B.	70	134	Para 2 Wt. 9-12	Rep. cysto. and recto., 1973 T.A.H. + B.S.O. + M.M.K., 1974 A&P rep.	7-30-74	11
12.D. D.	54	117	Para 2 Wt. 6-4	1958 V.H. rep. cysto & recto.	10-22-74	9

Williams[12] and Randall and Nichols[13] followed shortly. (The paper by Randall and Nichols appeared shortly before the first of the 12 patients reported below presented herself.) Tomlinson and Alexander[14] reported the use of a modified Dacron aortic bifurcation graft for this purpose.

Methods, results, and comments

Abdominal approach. The cases reported here were all subjected to a modification of the technique described by Randall and Nichols[13].

Patients with postmenopausal atrophy of the vaginal mucosa are treated preoperatively with oral and/or vaginal estrogens.

Operative technique. A Foley catheter is placed in the bladder. The patient is positioned on the operating table as for a suprapubic operation for urinary stress incontinence, i.e., supine, with the knees separated and partly flexed and supported on a pillow or rolled blanket, the ankles taped together. After routine surgical preparation, a sterile half-sheet is placed over the lower extremities. A curved ovum or sponge forceps bearing a tightly folded 4 by 4 gauze sponge is then inserted into the vagina, concave side anterior, to push the vaginal vault cephalad and anteriorly (Fig. 1). The handle of the forceps lies on the sterile half-sheet where it can be manipulated by the assistant through the laparotomy sheet placed over it.

The abdomen is entered through a Pfannenstiel incision. After manual exploration of the entire abdominal cavity, exposure is accomplished by means of an O'Sullivan-O'Connor retractor and upward packing of the bowel.

A transverse incision is made through the peritoneum covering the well-defined, easily accessible knob of vagina pushed upward. The vaginal knob is denuded of peritoneum anteriorly to the bladder reflection and posteriorly to the rectovaginal reflection of the enterocele sac. A vertical incision is then made in the peritoneum over the sacral promontory and carried downward 6 to 8 cm. A tunnel beneath the peritoneum of the cul-de-sac is developed by blunt finger and clamp dissection to reach the posterior vaginal wall. (In two of the reported cases the sigmoid colon was so voluminous that it was necessary to carry the vertical peritoneal incision over the sacrum all the way to the transverse one over the vaginal vault.)

A piece of polyester fiber mesh (Mersiline) is then prepared, approximately twice the width of the vaginal vault and 10 to 12 cm. long. This is folded longitudinally to make a double thickness and the edges are sutured together with 3 or 4 nonabsorbable sutures to maintain the layers in place. One end of this mesh strip is then sutured as far down as possible on the posterior surface of the denuded vaginal knob by a row of three interrupted sutures (of nonabsorbable, braided synthe-

tic material). A second row of three sutures is placed to attach the strip to the top of the knob. Care must be taken not to carry the sutures through the entire wall of the vagina into its lumen. Indeed, the reason for using six sutures to attach the mesh strip is to allow their superficial placement to avoid perforation of the vagina and yet insure a lasting attachment.

The forceps with sponge is then removed from the vagina and the other end of the mesh strip is pulled through the retroperitoneal tunnel by means of a kidney pedicle clamp as shown in Fig. 2. It is attached to the periosteum of the sacrum at about the level of the second or third vertebra by means of three interrupted sutures of the same synthetic material (only three are needed because of the strength and thickness of the periosteum). Excess mesh is cut away. Suspension of the denuded vaginal knob by the mesh strip tucks the vagina under the peritoneum of the cul-de-sac in such a way as to make recurrence of enterocele essentially impossible.

The peritoneal incisions are closed with continuous sutures of No.00 chromic surgical gut. The abdomen is closed in standard fashion. It has been customary to remove the Foley catheter and to start ambulation the morning after operation. Discharge from the hospital usually occurs on the fourth or fifth postoperative day.

Report of cases. Since adoption of the above abdominal operative procedure, it has been used for 12 patients. Table I presents the details of their cases. Their average age was 63, with a range of 52 to 72. All were parous, but there was no history of any traumatic delivery. Two had had babies over 9 pounds and three over 8 pounds, all delivered vaginally. At the time of surgery, the patients' weights ranged from 117 to 189 pounds.

This group of women had had multiple gynecologic surgical procedures, 10 of the 12 patients having had two or more operations. Six had had previous abdominal surgery designed to correct urinary stress incontinence; one had two such operations. Three had had a second operation primarily to correct vaginal vault prolapse, two of these by the abdominal route.

All of the patients gave a presenting complaint of protrusion from the vagina, and on examination the vaginal vault in all was found to be prolapsed beyond the introitus. The abdominal procedure was selected for these patients because all of them had a vaginal tube of normal caliber.

The most recent follow-up examination was carried out on six of the patients at from 9 to 23 months after operation, at more than 2 years for the other six patients. All vaginal vaults were in normal anatomical position high in the pelvis, some so high as not to be

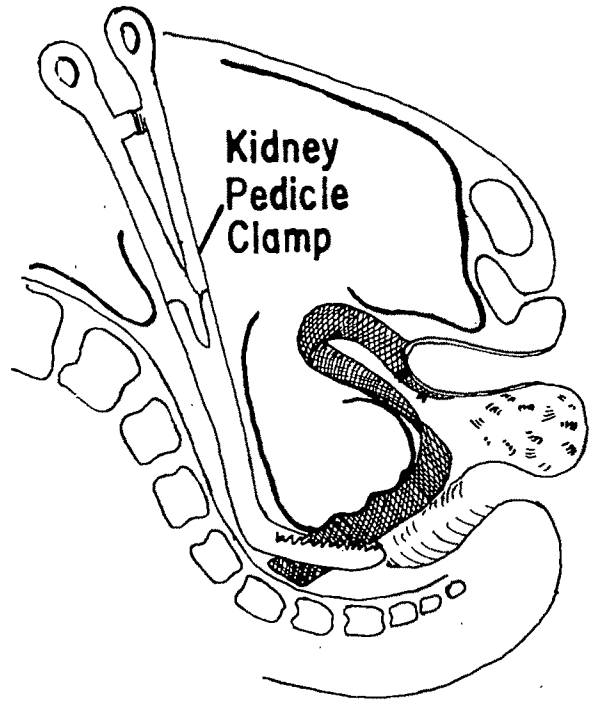


Fig. 2. Mesh pulled through peritoneum of enterocele to be followed by denuded vagina.

visible by usual bivalve speculum examination. No patient had any discernible enterocele. No patient had recurrence of urinary stress incontinence. One patient, at 22 months, had a minimal asymptomatic bulge between the vaginal vault and the urethrovesical area elevated previously by sutures for stress incontinence; it did not extend to the introitus. All patients have a functional vagina and some are engaging in coital function. One, more than 70 years old, enjoys coitus with orgasm two to three times a week with a 48-year-old male partner.

None of these cases had any significant morbidity, and no palpable pelvic masses or pelvic tenderness were found at follow-up examination.

Despite the somewhat limited and short experience with this surgical procedure, the results with it so far permit considerable enthusiasm about its facility and effectiveness.

Vaginal approach. The status of techniques for the repair of vaginal vault prolapse via the vaginal route is such that modifications presumed to be improvements continue to be proposed. Mengert's[7] unique study mentioned above demonstrated that the uterosacral ligaments did offer some support. Miller[15] reached through the opened vaginal vault, identified the uterosacral ligaments apparently by touch, and sutured them together. McCall[16] emphasized a technique for enterocele repair that involved opening both the vault

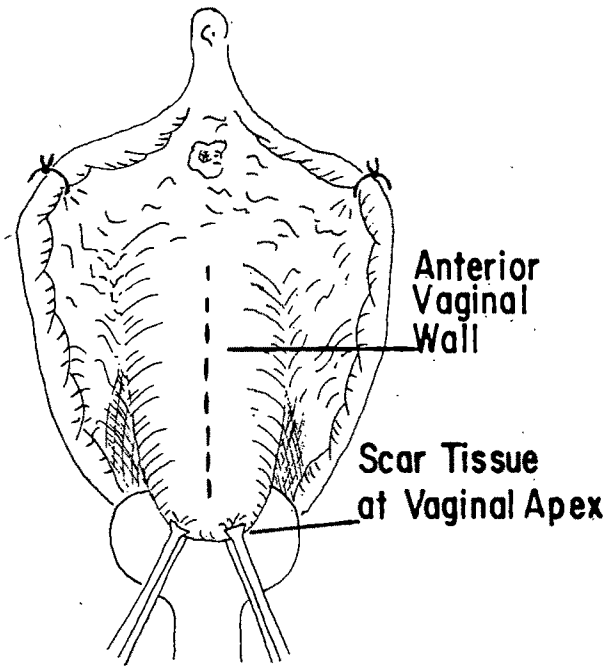


Fig. 3. With traction on vaginal apex, longitudinal incision is made through full thickness of vaginal wall.

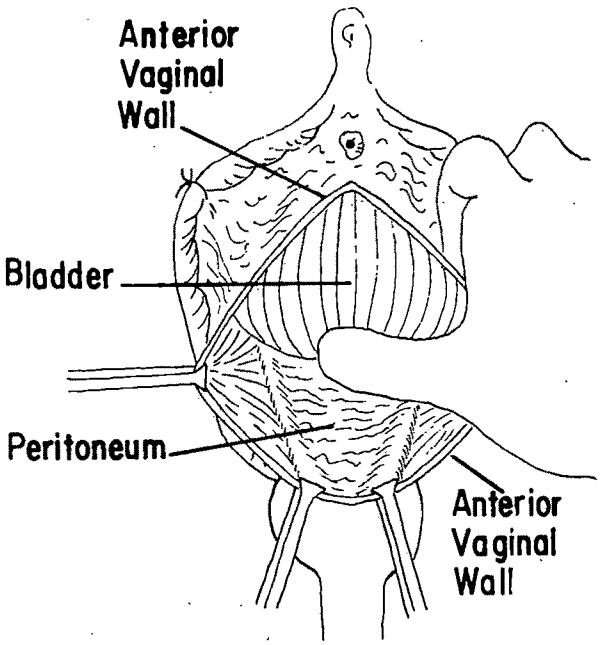


Fig. 4. Bladder advanced upward until peritoneum is exposed, also uterosacral ligaments identified.

and the cul-de-sac to suture the uterosacral ligaments together, but he apparently did not excise the peritoneal sac. He anchored the vagina behind the bridge thus formed. Symmonds[17] emphasized the importance of the uterosacral and the cardinal ligaments, but admitted that he often seemed to be simply

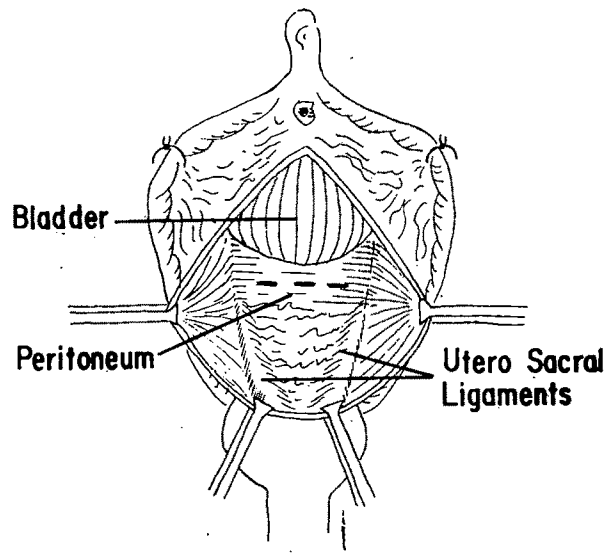


Fig. 5. Peritoneum is incised.

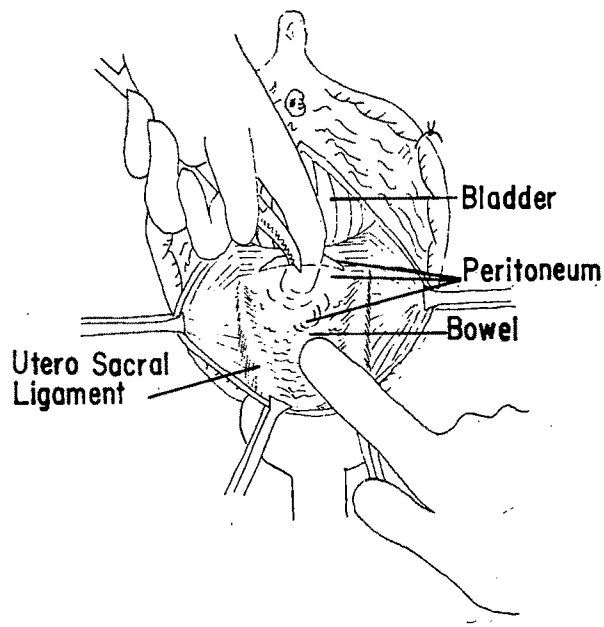


Fig. 6. Peritoneal (enterocele) sac is dissected free from vaginal wall and uterosacral ligaments back to bowel wall, and excised.

sewing "stuff to stuff." Ward[18] modified the Mayo technique for vaginal hysterectomy to include removal of the cul-de-sac peritoneum as a potential enterocele. He also identified the uterosacral ligaments and sutured them together back to the rectum.

The technique we are offering can be called "the anterior vaginal approach" for repair of vault prolapse. It is particularly advantageous for rendering discovery and utilization of the uterosacral ligaments and excision of the enterocele sac relatively easy.

Operative technique. The scar tissue of the vaginal

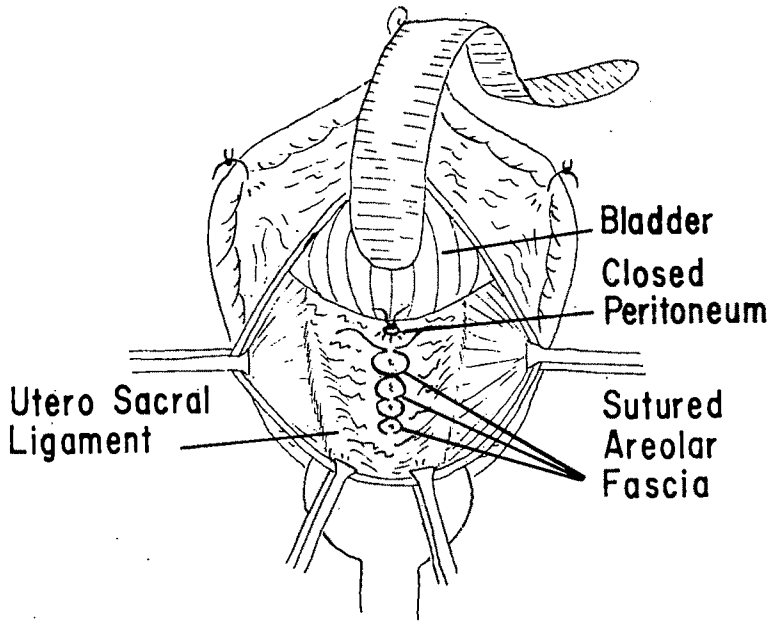


Fig. 7. Peritoneum is closed. Sutures placed in areolar fascia between bowel and uterosacral ligaments.

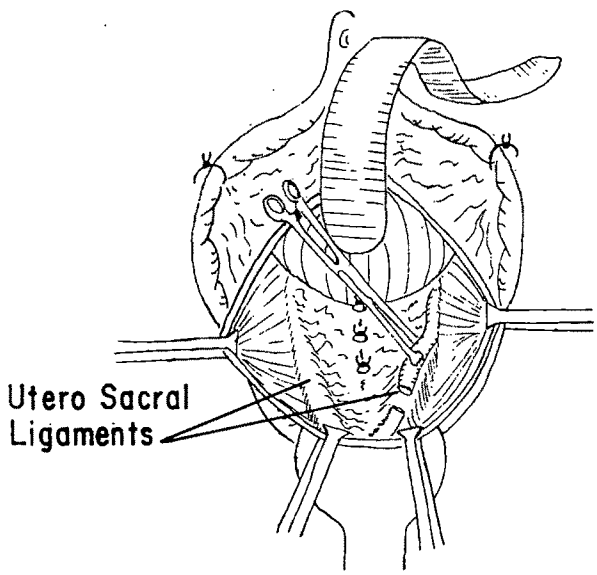


Fig. 8. Uterosacral ligaments are dissected from vaginal wall.

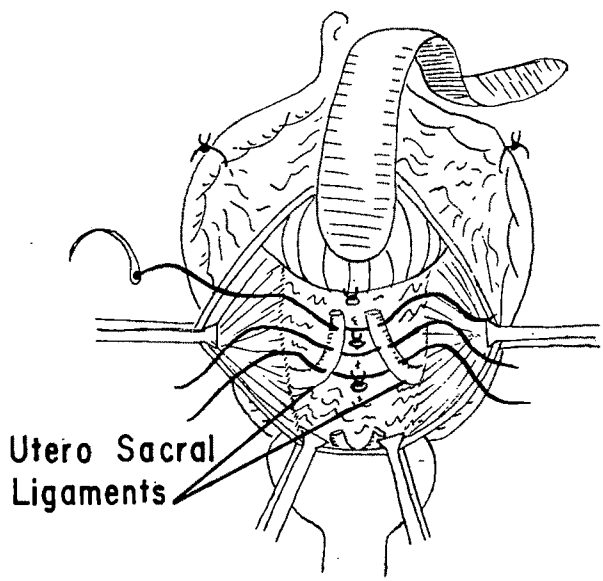


Fig. 9. Uterosacral ligaments sutured together under peritoneal purse string and repaired areolar fascia.

vault is grasped with two Allis clamps and drawn well out and down as in Fig. 3. The anterior vaginal wall is incised vertically and reflected laterally from the bladder and the urethra. Because of the scar tissue, advancement of the bladder until the peritoneum is seen may require some sharp as well as blunt dissection (Fig. 4).

Fig. 5 shows the site of incision of the peritoneum through which the pelvic area is then explored. With traction on the vaginal cuff the uterosacral ligaments can easily be identified.

One or more clamps are then placed on the posterior peritoneal edge and the peritoneal sac is dissected off the vagina and the uterosacral ligaments all the way back to its reflection from the bowel (Fig. 6). The muscularis of the colon is usually exposed. The peritoneal sac is then excised and its neck is closed with a purse-string suture.

By means of tissue forceps a layer of areolar fascia can be demonstrated on each side between the uterosacral ligaments and the bowel wall. These are sutured together in the midline with interrupted chromic sutures (Fig. 7).

The uterosacral ligaments—and probably some cardinal ligament components as well—are then grasped with one or two Allis clamps and dissected free from the vaginal wall at its posterior and lateral fornices (Fig. 8). Two to four mattress or figure-of-eight sutures are then used to plicate the ligaments under the peritoneal purse-string and areolar tissue sutures (Fig. 9).

The remainder of the operation proceeds along conventional lines. Mattress sutures plicate the vesicovaginal fascia, and Kelly plication is performed at the urethrovesical junction. Excess vaginal wall is excised, and the incision closed with a vertical suture line by means of full thickness figure-of-eight sutures. The vault is suspended to the united uterosacral ligaments with a mattress suture. Posterior vaginal repair of rectocele and perineorrhaphy are then carried out in standard fashion, emphasizing depth of rectocele repair and proper anatomical height of perineal body.

The technique described above as "the anterior approach" appears to have made vaginal repair of the prolapsed vault with cystocele and rectocele much easier to accomplish expeditiously and safely. Experience with the method used on seven cases is not yet extensive enough to permit an evaluation of results. It is hoped, however, that such evaluation may be hastened by trials of the technique by other gynecologic surgeons.

We are grateful to Carolyn Lee for the drawings and to Edmund W. Overstreet, M.D., for editorial suggestions.

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Discussion

Dr. Charles P. Langmade, Pasadena, California. No less an authority than Victor Bonney once stated that no operation would correct vaginal vault prolapse without shortening the vagina. That was many years ago, yet still holds true today. Dr. Rust, however, presents 12 cases without failure or shortening and he is to be congratulated.

The operative treatment of vaginal vault prolapse does present a major challenge to the gynecologist's skill. Prolapse of the vault following abdominal or vaginal hysterectomy, even with the most meticulous attention to the cardinal ligaments, uterosacral ligaments and cul-de-sac, does occur. The inherent weakness Dr. Rust describes is a true entity. We all blame ourselves or others for failure to prevent vault prolapse, yet many of these patients previously have had inguinal, femoral and umbilical hernias repaired.

Dr. Rust states that colpocleisis is an almost historical operation and to this we disagree. If there is a patient in whom vaginal vault prolapse can be avoided, it is in the 70- to 75-year-old widow with no sexual activities for 20 years and none planned. A properly done colpocleisis with careful attention given to a small space left between the anterior and posterior walls will leave a nonfunctioning vagina, no stress incontinence, and no postoperative vaginal vault prolapse. Many excellent men agree there is no place for colpocleisis; however, Dr. Hofmeister disagrees and states many elderly patients benefit a great deal from this operation and to this we agree.

Dr. Rust summarized very well the work of many men who have struggled with this problem through the years. Dr. Henry Shaw, during my medical school days, was the first to admit that with a poor anterior abdominal wall his operation would fail. Dr. Randall's technique was modified for the present series of cases. Twelve cases followed without failure; 9 to 23 months in one group and over 2 years in the second group. Certainly this is an excellent achievement and suggests very good results for the future. I agree with Dr. Rust's enthusiasm.

The use of the anterior approach for the large vagina and the abdominal approach for the small vagina is an interesting concept. The large bulging vaginal vault prolapse with a large enterocele, cystocele, and rectocele have no uterosacral or cardinal ligaments, and what is sutured as uterosacral ligaments

is a fold of peritoneum in the area of the uterosacral ligaments, as Dr. Symmonds so aptly puts it, "suturing stuff to stuff." The anterior approach without shortening the vagina and without additional vault support from above in my opinion will not lead to lasting support.

Dr. Rust alluded to the problem of infection with the use of synthetic strips and probably for this reason does not wish to combine the synthetic strip with the anterior approach and the open vaginal vault. This is one advantage of fascial strips as used by Dr. Beecham or Cooper ligament strips. No complications have been encountered since 1965 with the Cooper ligament strips and Dr. Beecham reports none with his homologous fascia lata strips. Dr. Rust also has had no complications and his patients are discharged from the hospital in a remarkably short time.

In evaluating results, it comes to mind that one failure in the next few cases would give an approximate 10 per cent failure rate. This is not my thinking, however, and it is my sincere hope there will be no failures or complications and if so, Dr. Rust has shown us a very good approach to a problem we all face.

DR. RICHARD L. TAW, Los Angeles, California. I would remind you of a couple of anatomical facts. If you remember the diagrams that Dr. Rust presented, the uterosacral ligaments were demonstrated as being horizontal when the patient was in the lithotomy position. When you have a severe situation as this, the uterosacral ligaments are extremely difficult to identify. They are actually in a vertical position and they go back downward instead of horizontally toward the ureters.

The second thing is that if there is prolapse of the vault to any extent at all, including the bladder, there is also prolapse of the ureters in the lateral pelvic wall, and that anyone doing surgery in this area using the uterosacral ligaments, without first identifying the ureters, sooner or later is going to find themselves in serious trouble.

The last thing I would like to mention is that mersilene is not necessarily a totally inert material. In the last two years I have had the opportunity to remove either mersilene mesh or tape because of a ligneous connective tissue reaction to this material, and in one case it actually obstructed the ureter.

DR. WARREN E. JONES, Sacramento, California. Dr. Rust has ably presented the two major approaches most commonly used by gynecologists in the management of posthysterectomy vaginal vault prolapse, and he indicates a number of variations, including the anterior vaginal approach to the enterocele.

My own preference is for Pratt's method of using the scar of the vaginal vault as one would use the cervix in a vaginal hysterectomy, thus identifying the enterocele sac and removing it and at the same time exposing the uterosacral ligaments. Or, in the patient who has a narrowed introitus due to previous vaginal repair and where a midline perineotomy is advantageous, I approach the enterocele through a midline incision in the posterior vaginal wall.

However, not all patients will be suitable for the two major approaches described by Dr. Rust. Rarely, we will need other methods to correct vaginal vault prolapse. One such alternative was called to our attention by the 1971 article by Randall and Nichols.[1] This vaginal method was first described by Zwiefel in 1892 and in subsequent years at least five other authors have published reports on variations in the method, though several of the papers have been in the German literature.

Randall points out that after removing the enterocele sac and closing the peritoneum at a high level by means of a purse string, starting well up on the anterior rectal wall, when the uterosacral ligaments are of minimal or negligible strength, the vaginal vault, after anterior repair of the vagina, can be sutured transvaginally to the right sacrospinous ligament under direct vision.

The approach is through the rectovaginal space, through the right rectal pillar into the pararectal space and to the ischial spine. Then with appropriate long and narrow retractors it is possible to elevate the bladder and ureter out of the way and to place the sutures through the ligament under direct vision, bringing them out through the vaginal vault. When the sutures are tied, the vault is fixed to the sacrospinous ligament, restoring the normal horizontal axis of the upper vagina.

We have used this procedure in three patients since 1971 and have obtained excellent results in all. In addition, there was good vaginal depth.

Finally, I would agree with Dr. Langmade that there is, indeed, a place for subtotal vaginectomy in the older patient with fragile tissues and who is no longer desirous of coital function. This method was beautifully presented at our Society's meeting in Portland in 1962 by our late colleague, William Bradbury.[2]

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DR. GILBERT A. WEBB, San Francisco, California. I would like to emphasize Dr. Rust's statement, namely to use a synthetic material when you are suturing the mersiline mesh in place. The vascular surgeons demonstrated quite awhile ago that silk or cotton does not react well with the mersiline. Therefore the sutures may fall out. I have seen one instance where silk sutures were used. The vault prolapsed within weeks. At the time of reoperation the mesh was just sitting there, the sutures having dissolved. Use of mersiline

sutures with the mersiline mesh will prevent this problem.

In our hospital we have had two complications with this type of repair, one of them a very serious one. In the first case, the mersiline mesh was sutured to the anterior spinous ligament. The patient developed an infection which went through the lymphatics into the subarachnoid space. The patient ended up with a brain abscess.

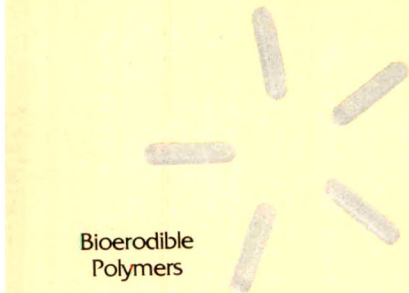
I would like to re-emphasize what Dr. Rust said, not to combine a vaginal procedure requiring opening the peritoneal cavity with the abdominal procedure. In the other case this was done inadvertently by opening into a large enterocele during the posterior repair to correct a large rectocele. An infection ensued with the mersiline acting as a foreign body. This had to be removed approximately 1 year later.

DR. RUST (Closing). Dr. Jones mentioned his experience with the vaginal operation also described by Randall in which he sutured the vault to the right sacrospinous ligament. I have not tried it, but would like to see it done. I am sorry I overlooked mentioning it in my review of the literature.

Apparently there is a different opinion as to the various colpocleisis operations. Like such operations as the Manchester-Fothergill and the Watkins transposition, there no doubt is an occasional indication. Our aim is to preserve the vagina as a usable structure even though the patient professes never to want to use it again. I would prefer the vaginal pessary, my favorite is the Gelhorn, to obliteration.

Both Drs. Langmade and Taw questioned the presence of uterosacral ligaments in prolapse of the vaginal vault. My drawings were made from actual photographs. The reason for presenting our vaginal approach was to show the way to find and utilize them. The anatomy is about the same as seen at vaginal hysterectomy for prolapse, after the uterus has been removed. Hunting for them in the usual upward extension of the posterior colporraphy is frustrating.

If there is a recurrence after our vaginal operation, we will resort to the sacral colpopexy.



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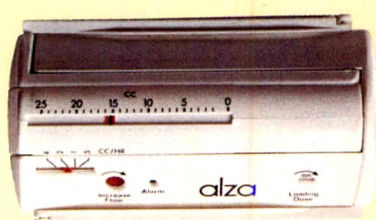
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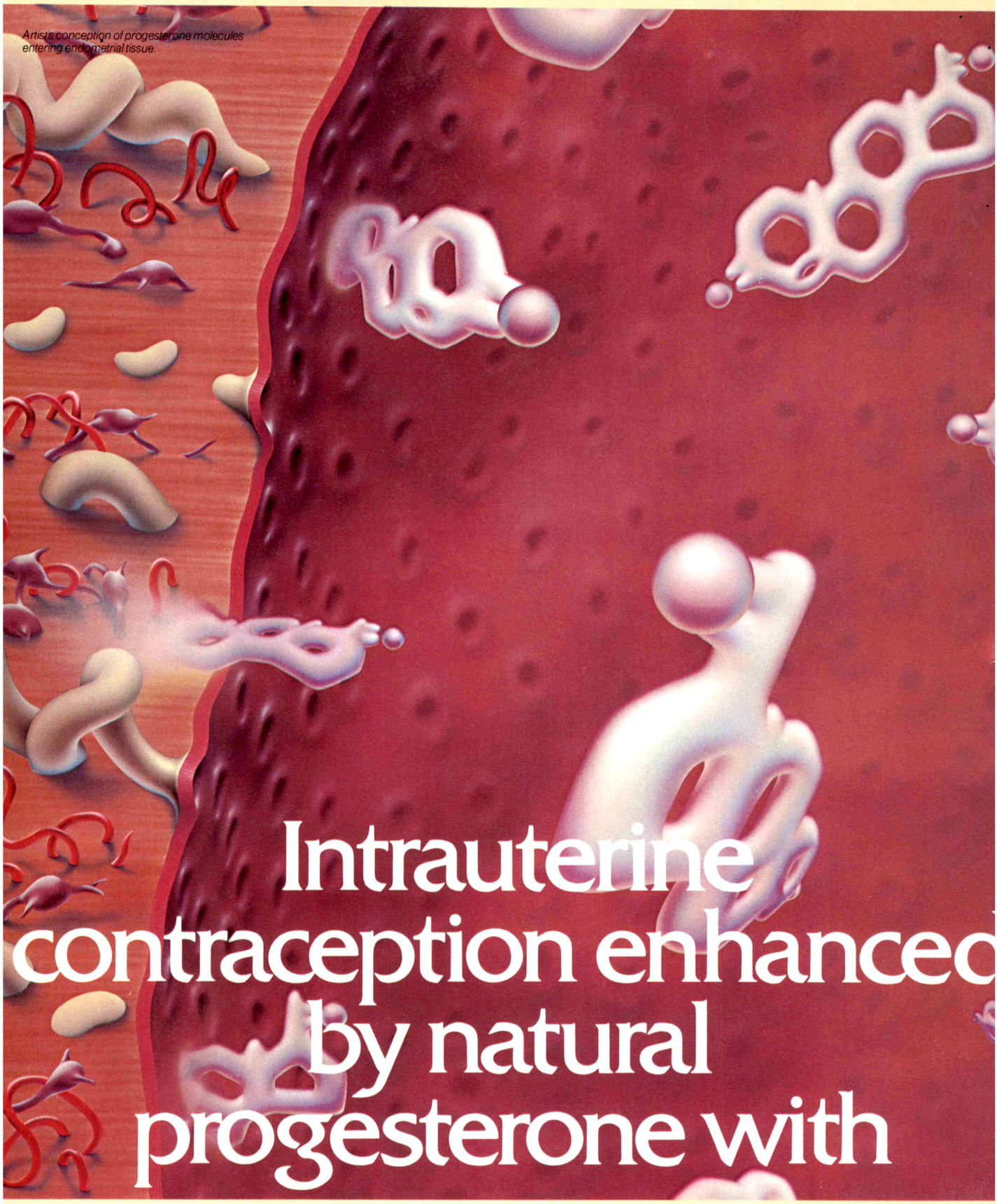
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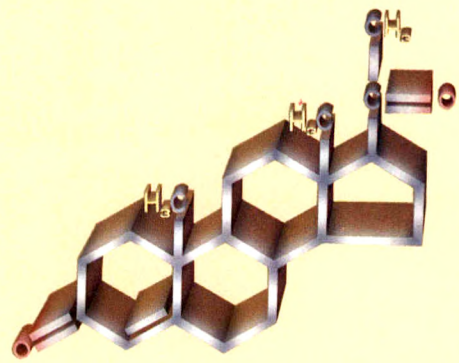
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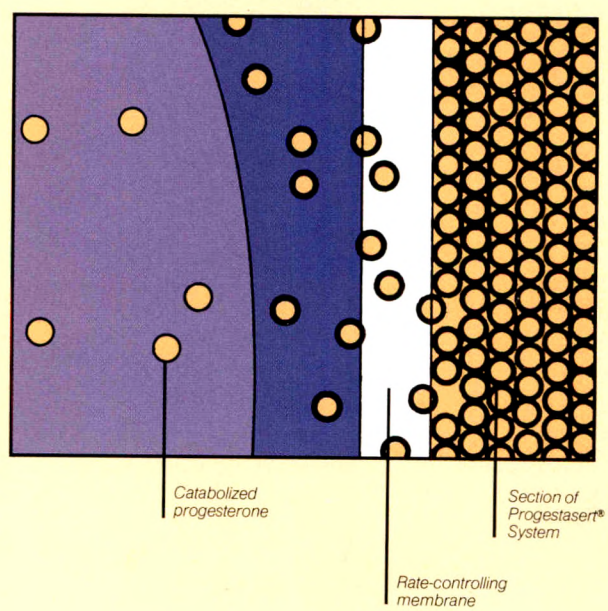
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The total quantity of progesterone contained in one Progestasert® System for one year's use is only 38 mg— less than the amount produced in one day by the corpus luteum during the latter part of the menstrual cycle. The amount of progesterone released daily from the System corresponds to a small percentage of the daily physiologic production.



A unique drug delivery system

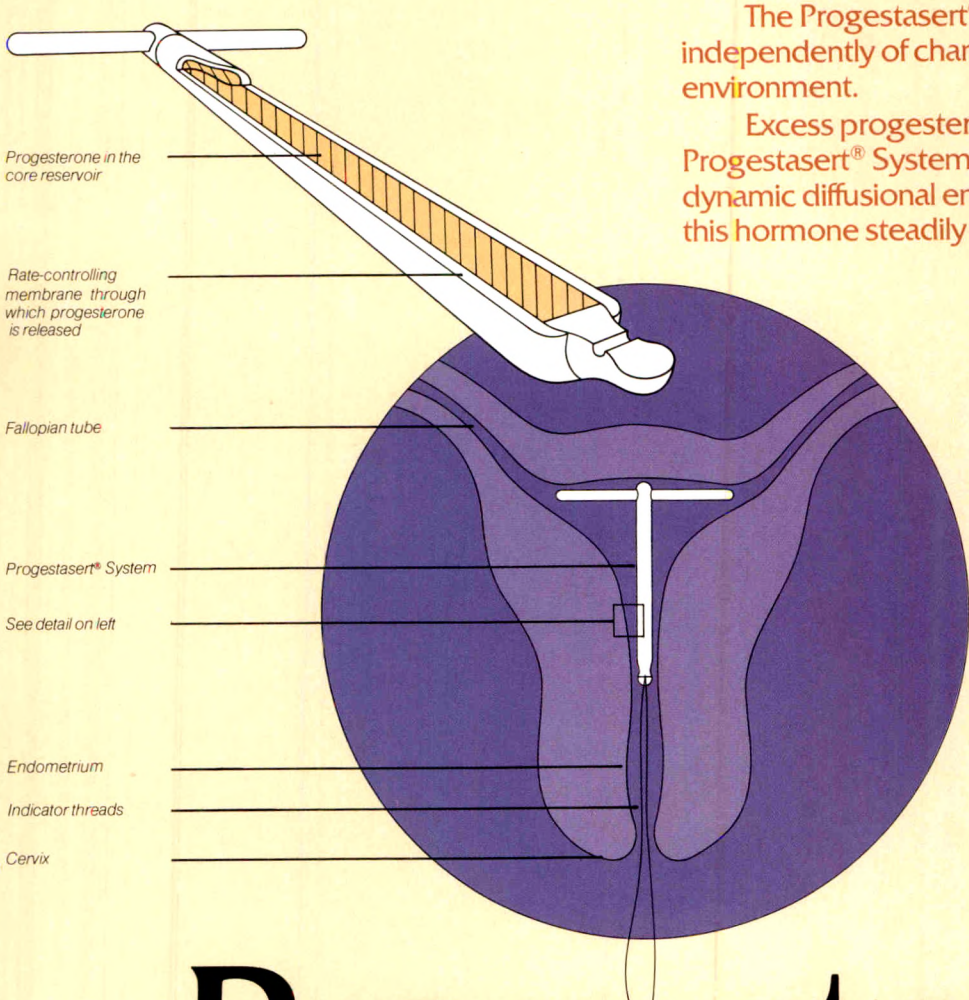
The Progestasert® System is a diffusional system designed to deliver microquantities of progesterone. The two key components are:

- ☐ a core reservoir of progesterone crystals with barium sulfate (for radiopacity) in medical-grade silicone oil
- ☐ an inert diffusional membrane of ethylene/vinyl acetate copolymer that surrounds the core reservoir and provides programmed control of progesterone release

When the Progestasert® System is placed in the uterine environment, progesterone molecules diffuse through the membrane into the uterine lumen at the average rate of 65 micrograms per day for one year.

The Progestasert® System functions independently of changes in the uterine environment.

Excess progesterone within the Progestasert® System provides the thermodynamic diffusional energy needed to release this hormone steadily for an entire year.



WHY THE T CONFIGURATION?

A T-shaped configuration was selected to contain the progesterone reservoir because this configuration has shown:*

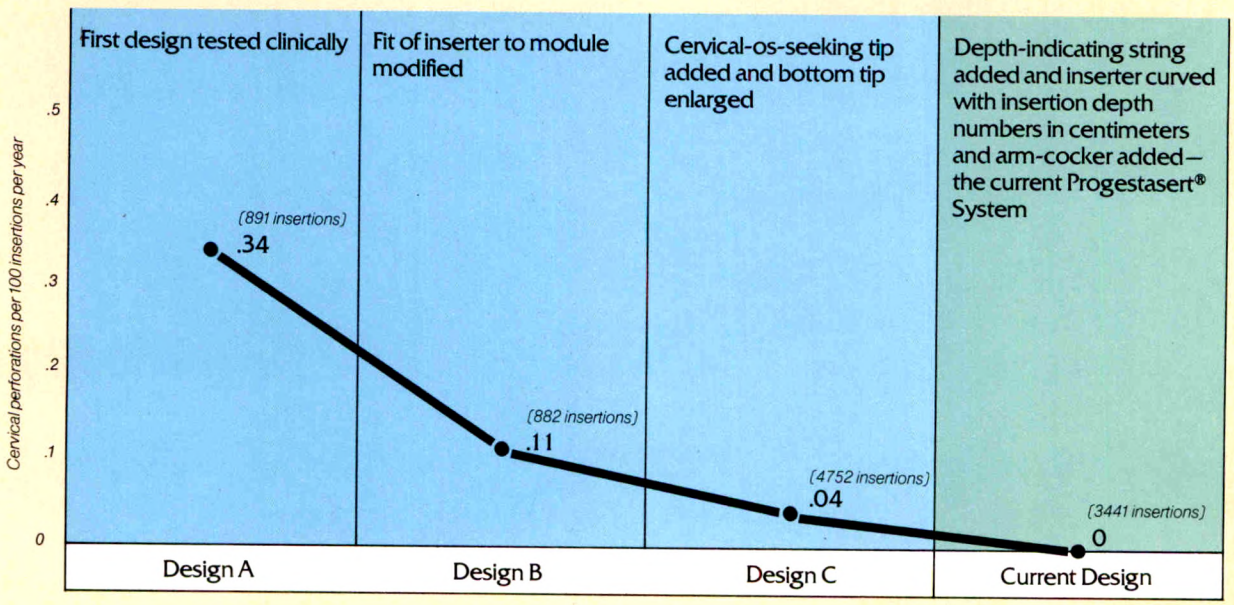
- ☐ easy insertion
- ☐ excellent retention by the uterus
- ☐ minimal symptomatic evidence of uterine irritation
- ☐ easy removal

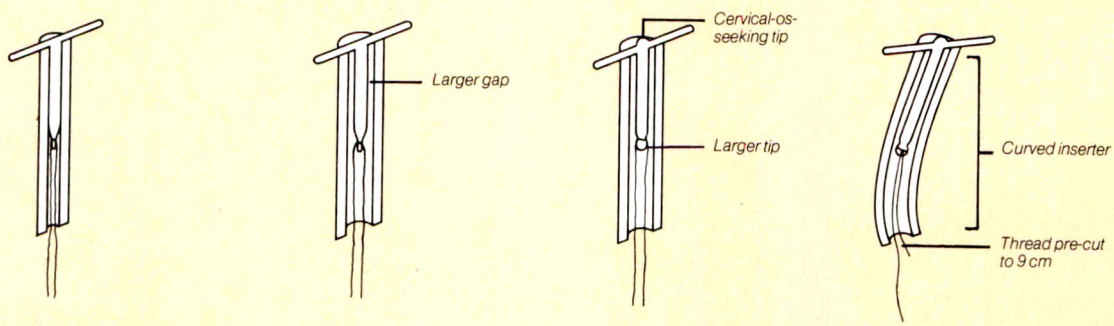
*Tatum HJ: Intrauterine Contraception. American Journal of Obstetrics and Gynecology, 112: 1000, 1972.

Progestasert®

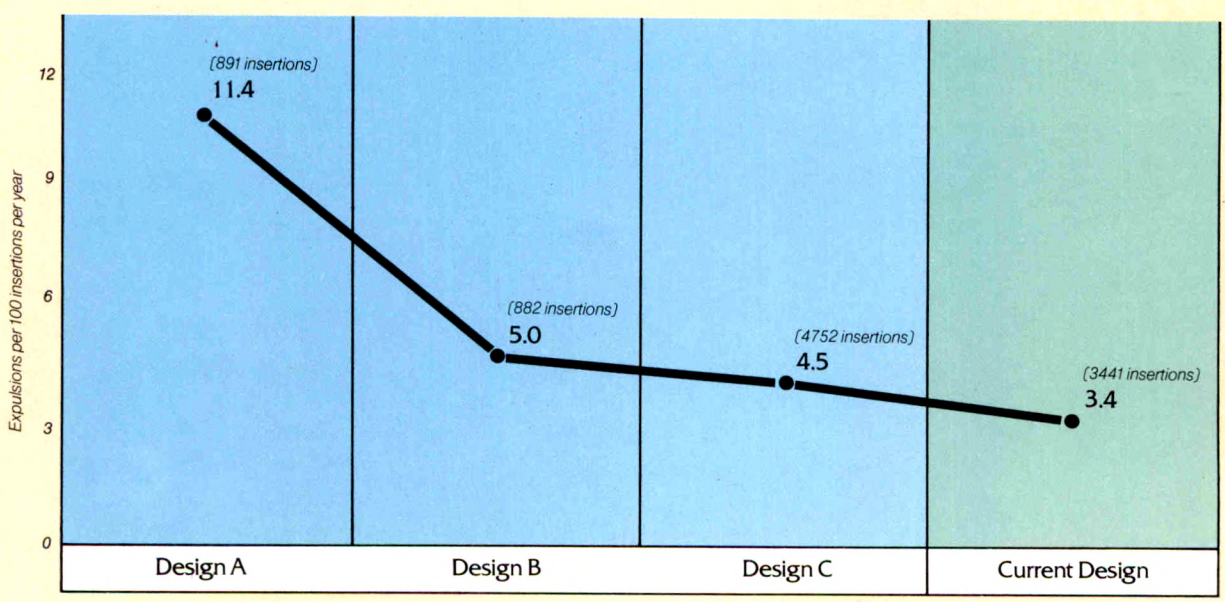
Intrauterine Progesterone Contraceptive System

CERVICAL PERFORATIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED





EXPULSIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED



These graphs do not represent a comparison of inserters produced by different manufacturers. Rather, they depict stages in ALZA's development

All numbers are expressed as events per 100 women per year.

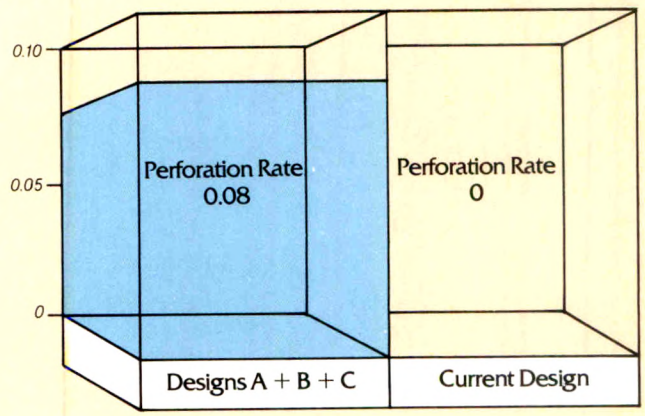
Inserter designed for safety and effective placement

As recently noted by Mishell, inserter design is increasingly recognized as important to the efficacy and safety of intrauterine contraceptive devices. "Proper placement...is of extreme importance for IUD effectiveness... (Thus), more attention should be directed toward the development of optimal IUD inserters than to changes in the IUD design."*

Some untoward effects with intrauterine devices—such as perforation and expulsion—in the past have been due to difficulties in placement. Since the technique of insertion and correct high fundal positioning play an important role in assuring contraceptive effectiveness and patient comfort and safety, much attention has been directed toward the development of the Progestasert® System inserter.

In controlled studies, evolutionary changes in the inserter and the Progestasert® System have demonstrated a decrease in the incidence of expulsions, cervical perforations, and uterine perforations which have paralleled these design changes. The incidence for both cervical and uterine perforations has decreased to the point that neither type of perforation has occurred with the 3,441 insertions with the final design after an average of more than nine months of exposure for these women.

UTERINE PERFORATIONS REDUCED AS ALZA'S SYSTEM AND INSERTER DESIGN IMPROVED



While these data reflect the importance of the design changes, the lack of perforations during these limited trials in no way suggests the Progestasert® System and its inserter will be trouble-free in general use. Perforations, both cervical and uterine, may occur with the Progestasert® System as its use becomes more widespread. The rate of perforation will depend upon anatomical and physiological variations of the women receiving the System and the care taken during the insertion process.

Progestasert®

Intrauterine Progesterone Contraceptive System

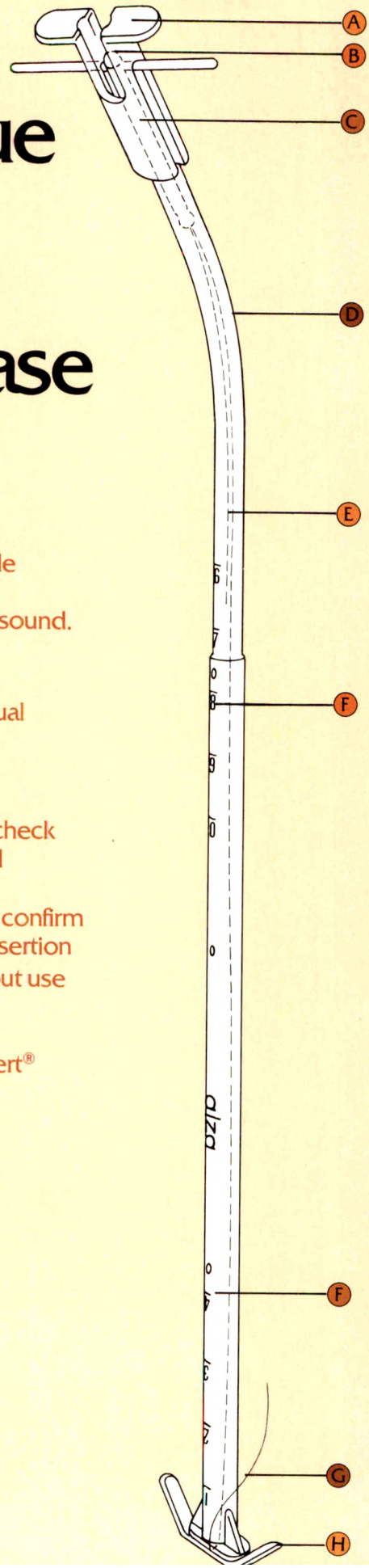
The System and its unique inserter-designed for safety and ease of insertion

The Progestasert® System inserter facilitates correct System placement while minimizing the risk of perforation, and is designed to function much like a uterine sound.

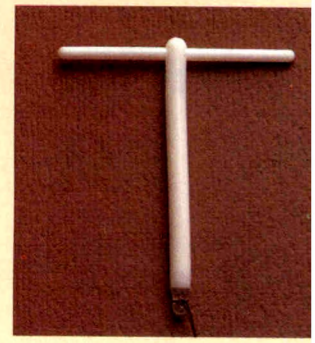
Features of the inserter:

- ☐ pre-curvature to facilitate insertion
- ☐ malleability for adapting to the individual uterus
- ☐ dual checking mechanism for correct placement
  - — centimeter markings on inserter to check conformity with previously sounded uterine depth
  - — indicator thread length designed to confirm proper System position following insertion
- ☐ high fundal placement achieved without use of plunger or push-rod

Comprehensive illustrated insertion instructions are a part of every Progestasert® System package.



Actual Size



A. Arm-cocker allows the arms of the T to be folded aseptically, using one-handed technique just prior to insertion.

B. Cervical-os-seeking tip helps guide the System into the cervical canal, making insertion easier and more comfortable.

C. Vertical stem of the System designed with flexibility and rounded tip to minimize cervical perforation risk.

D. Curved portion of inserter designed to conform to anatomic configuration of most cervical-uterine cavities. Malleability allows accomodation to variations in uterine anatomy.

E. Indicator monofilament thread, extended 9 cm from the top of the System, verifies correct placement at insertion.

F. Graduations (in centimeters) to determine uterine position and depth, and to confirm correct System placement.

G. Retainer monofilament thread extends the length of the inserter and is anchored by the thread-retaining plug to retain the System in the inserter.

H. Thread-retaining plug is removed to release the System in the uterus.

Safety studies

Clinical safety studies demonstrated:

- No extrauterine metabolic or endocrine effects in humans*
- Endometrial changes induced by the Progestasert® System disappear within weeks after System removal
- Rapid return to fertility confirmed in women discontinuing use of the Progestasert® System in the hope of becoming pregnant. The cumulative conception rate among 154 women was 49 per 100 women pregnant at 3 months after removal, and 76 per 100 women at 12 months after removal. These rates of return to fertility are similar to those reported following removal of an IUD.

Effective contraception for one year from a single placement

The Progestasert® System functions unattended for one year at a continuous release rate of 65 micrograms of progesterone per day, eliminating reliance on daily hormone administration.

Yearly removal and placement can coincide with annual visits for physical examination and Pap smear, as encouraged by the American College of Obstetrics and Gynecology. (Currently accepted practice used by recognized authorities, reported in ACOG Technical Bulletin #29, February, 1975, p 7.)

Progestasert®

Intrauterine Progesterone Contraceptive System

Some clinical aspects

Data were collected in 40 clinics involving 5,495 women over a period of 45,848 woman-months. These trials were designed to obtain data that would predict the true use-effectiveness of the System.

HIGHLY EFFECTIVE INTRAUTERINE CONTRACEPTION

Clinical results have demonstrated pregnancy rates of 1.9† in parous patients and 2.5† in nulliparous patients. A similar T-shaped unit, but without progesterone in the stem, produced a pregnancy rate of 18.3†.

HIGH DEGREE OF ACCEPTABILITY

Clinical studies have demonstrated a high continuation rate. Approximately 8 of every 10 parous and 7 of every 10 nulliparous women continued use of the Progestasert® System for a full year.

SHAPE PROVIDES EXCELLENT RETENTION

Expulsion rates of 3.1† and 7.5† were observed for parous and nulliparous women respectively.

INSERTER PROVIDES SAFE PLACEMENT

No uterine perforations have occurred with 3,441 insertions using the current pre-curved, malleable inserter during controlled clinical trials. This should not be interpreted as a guarantee that perforations will not occur with the Progestasert® System.

	Parous	Nulliparous
PREGNANCY RATE	1.9	2.5
EXPULSIONS	3.1	7.5
CONTINUATION RATE	79.1	70.9

Features and benefits

- ☐ Contraception provided by progesterone, identical to the natural ovarian hormone
- ☐ No known systemic hormonal effects*
- ☐ Continuous delivery of progesterone in microgram amounts/day
- ☐ Effective contraception for one year from one System placement
- ☐ High degree of patient acceptability
- ☐ Excellent uterine retention
- ☐ Minimal reliance on patient compliance during its year of use when compared to extrauterine contraceptives
- ☐ Prompt return to pre-insertion fertility following System removal
- ☐ Inserter designed for safety and ease of insertion

Candidates for the Progestasert® System

THE NEW CONTRACEPTIVE USER

The natural progesterone contraception provided by the Progestasert® System without systemic hormonal effects, along with minimal dependence on patient compliance, small unit size, and easy insertion, make the Progestasert® System an attractive first contraceptive for many women.

THE NONCOMPLIER

The daily regimen of pill-taking proves beyond the capability of some patients for whom hormonal contraception is preferable. The Progestasert® System reduces requirements for patient compliance to once-a-year replacement.

THE PATIENT DISCONTINUING ORAL CONTRACEPTIVES

Patient-initiated— the Progestasert® System offers the opportunity to continue hormonally enhanced contraception without the adverse systemic hormonal effects* that cause many women to dicontinue oral contraceptives.

Physician-initiated— some physicians consider it important for the patient to discontinue oral contraceptive use until the body regains its normal hormonal balance. Some physicians discontinue the Pill permanently. Recent studies strongly suggest that oral contraceptive users are at greater risk of developing coronary thrombosis than nonusers. The Progestasert® System, with its lack of adverse systemic hormonal effects,* can be the desired alternative contraceptive for former users of the Pill.

THE PATIENT DISCONTINUING OTHER CONTRACEPTIVE METHODS

The inconvenience and lower efficacy rates of diaphragms and condoms make the Progestasert® System an attractive alternative for the patient desiring intrauterine hormonal contraception without systemic hormonal effects.*

THE IUD PATIENT DUE FOR REINSERTION

For those patients already using some form of intrauterine contraception, the Progestasert® System, designed for safety, offers an effective alternative to their present IUD and may be considered at reinsertion time.

Progestasert®

Intrauterine Progesterone Contraceptive System

Ordering Information

IF YOU WOULD LIKE FURTHER INFORMATION ABOUT ALZA, THERAPEUTIC SYSTEMS, THE PROGESTASERT® SYSTEM, DETAILED INSERTION INSTRUCTIONS OR WOULD LIKE TO ORDER PROGESTASERT® SYSTEMS FOR YOUR PRACTICE, CALL THE FOLLOWING TOLL-FREE NUMBER: (800) 227-9953 OR WRITE TO ALZA PHARMACEUTICALS, 3170 PORTER DRIVE, PALO ALTO, CALIFORNIA 94304.

Progestasert®

Intrauterine Progesterone Contraceptive System

Release rated 65 μg/day progesterone for one year.

DESCRIPTION

The Progestasert® Intrauterine Progesterone Contraceptive System is a white, T-shaped unit constructed of ethylene/vinyl acetate copolymer (EVA) containing titanium dioxide. The 36 mm tubular vertical stem of the T contains a reservoir of 38 mg of progesterone, USP, together with barium sulfate, USP, for radiopacity; both are dispersed in medical grade silicone oil. The 32 mm horizontal crossarms are solid EVA. Two monofilament nylon indicator/retrieval threads are fastened to the base of the T stem. The Progestasert® system is packaged sterile within its curved, malleable inserter. Progesterone is released from the system at an average rate of 65 μg/day for one year by membrane-controlled diffusion from the reservoir. None of the inert ingredients of the reservoir or membrane—barium sulfate, silicone oil, titanium dioxide, or EVA—is released from the system.

ACTION

Available data indicate that the contraceptive effectiveness of the Progestasert® system is enhanced by its continuous release of progesterone at an average rate of 65 μg/day into the uterine cavity. The mechanism by which progesterone enhances the contraceptive effectiveness of the T is local, not systemic. The concentration of luteinizing hormone, estradiol, and progesterone in systemic venous plasma follow regular cyclic patterns indicative of ovulation during use of the Progestasert® system. Blood chemistry studies related to liver, kidney, and thyroid function also reveal no changes.

During use of the system, the endometrium shows progestational influence. Following removal of the system, the endometrium rapidly returns to its normal cyclic pattern and can support pregnancy. The local mechanism by which continuously released progesterone enhances the contraceptive effectiveness of the T has not been conclusively demonstrated. The hypotheses that have been offered are: progesterone-induced inhibition of sperm capacitation or survival, and alteration of the uterine milieu so as to prevent nidation.

INDICATION

The Progestasert® system is indicated for contraception.

CONTRAINDICATIONS

Pregnancy or suspicion of pregnancy; abnormalities of the uterine cavity; acute pelvic inflammatory disease or history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past 3 months; uterine or cervical malignancy; unexplained genital bleeding until suspicion of cancer is ruled out; acute cervicitis.

WARNINGS

A. Pregnancy

1. Septic abortion. Recent reports have indicated an increased incidence of septic abortion, associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an intrauterine device (IUD) in place. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Progestasert® system in situ, it should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the system remains in situ, she shall be warned of the increased risk of sepsis and be followed with close vigilance.
2. Congenital anomalies. Systemically administered sex steroids, including synthetic progestational agents, have been associated with an increased risk of congenital anomalies including cardiovascular anomalies. Such effects have not been reported with progesterone itself, which is produced in large concentrations during pregnancy.
3. Ectopic pregnancy. A pregnancy that occurs while a patient is wearing an IUD is much more likely to be ectopic in nature. Therefore, such patients in whom pregnancy occurs should be carefully evaluated.

B. Severe Pelvic Infection

Occasionally serious pelvic infection may occur with an IUD in situ. Under such circumstances the IUD should be removed, appropriate bacteriological studies done, and appropriate antibiotic treatment instituted.

C. Perforation

Perforation of the uterus may occur. If this occurs, the device should be removed. Local inflammatory reaction with abscess formation is a possibility if an IUD is left in the abdomen. Cervical perforation, often asymptomatic, has also been reported. If such occurs, the device should be removed.

PRECAUTIONS AND ROUTINE EXAMINATIONS

A. Patient Examination

The physician should make a determination that the patient is not pregnant. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed during or shortly following a menstrual period. The system should not be inserted postpartum or postabortion until involution of the uterus has been completed. Prior to insertion, a pelvic examination, pap smear, and gonorrhea culture should be done. Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The patient should be told that some bleeding or cramps may occur during the first few days after insertion. If these symptoms continue or are severe, she should report to her physician. She should be cautioned not to pull on the threads, which would displace the system.

B. Requirements for Continuation and Removal

The Progestasert® system must be replaced each year. There is no evidence of decreasing contraceptive efficacy with time before one year, but the contraceptive effectiveness of the Progestasert® system after one year has yet to be established. Therefore, the patient should be informed of the known duration of the contraceptive efficacy and be advised to return in one year for re-examination, removal and possible reinsertion.

The Progestasert® system should be removed for the following medical reasons: Menorrhagia and/or metrorrhagia producing anemia; uncontrolled pelvic infection; intractable pain, often aggravated by intercourse; pregnancy, if the thread is visible; uterine or cervical malignancy; uterine or cervical perforation; an increase in length of thread extending from the cervix, or any other indication of partial system expulsion.

C. Continuing Care of Patients Using the Progestasert® System

Patients should be re-examined and evaluated within three months after Progestasert® system insertion.

Routine annual examination, removal of the Progestasert® system, and reinsertion of a new Progestasert® system along with appropriate medical and laboratory evaluation should be carried out.

ADVERSE REACTIONS

Reported adverse reactions include: Endometritis, spontaneous abortion, septic abortion, septicemia, perforation of uterus and cervix, pelvic infection, cystic masses in pelvis, abdominal adhesions, intestinal obstruction, cervical erosion, vaginitis, leukorrhea, cystitis, pregnancy, ectopic pregnancy, uterine embedment, difficult removal, complete or partial expulsion, intermenstrual spotting, prolongation of menstrual flow, anemia, amenorrhea or delayed menses, pain and cramping, backaches, dyspareunia, leg pain or soreness, weight loss or gain, nervousness, bradycardia and syncope secondary to insertional pain.

DOSAGE AND ADMINISTRATION

A single Progestasert® system is to be inserted into the uterine cavity (see Precautions section). Present information indicates that the contraceptive effectiveness of the system is retained for one year and the system must be replaced one year after insertion.

HOW SUPPLIED

Available in cartons containing six sterile systems (Progestasert® system with an inserter).

CLINICAL STUDIES

Different event rates have been recorded with the use of different contraceptive methods. Inasmuch as these results are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and do not discontinue due to adverse reactions or pregnancy. In clinical trials sponsored by Alza with the Progestasert® system, use-effectiveness was determined for parous and nulliparous women by the life table method. (Rates are expressed as events per 100 women through 12 months of use.) This experience is based on 45,848 woman-months of use with 5,495 women, of whom about 25% were nulliparous; 2,157 women completed 12 months of use.

	Parous	*Nulliparous*
Pregnancy	1.9	2.5
Expulsion	3.1	7.5
Medical Removals	12.3	16.4
Continuation Rate	79.1	70.9

CAUTION

Federal law prohibits dispensing without prescription.

alza

Benign cervical and vaginal changes associated with exposure to stilbestrol in utero

EUGENE C. SANDBERG, M.D.

Stanford, California

Examinations of 320 young women allegedly exposed to stilbestrol in utero have revealed at least 12 unique and benign variations from normal anatomy, five in the cervix and seven in the vagina. Over two thirds of the patients revealed one or more of these variations. Some have been previously reported, others have not. None changed significantly or deleteriously during observation. All are described and a representative drawing of each is included. A classificational nomenclature is offered. It is felt that familiarity with these changes will allow presumptive identification by simple pelvic examination of at least two thirds of females exposed to stilbestrol in utero.

IN THE PROCESS of examining 320 young women, all of whom were alleged to have been exposed to stilbestrol in utero, a number of benign anatomical variations in the area of the cervix and the vagina have been observed. The vast majority appear to be the result of embryologic exposure to stilbestrol as exceptionally few of them have been observed in unexposed patients. Some have been reported in the recent literature by other observers of patients with similar exposure. Others have not.

The terms employed by previous authors to describe some of these changes include the following: transverse vaginal and cervical ridges (partial septa),[1–3] cervical pseudopolyp,[1–4] strawberry cervix,[5] cervical cock's-comb-like lesion,[3, 5, 6] endocervical lesion,[5] erythroplakia,[6] snub-nose-like cervices,[2] vaginal pericervical collar,[1, 2] vaginal hood,[5, 6] vaginal adenosis,[1–3, 6, 7] vaginal firm band,[7] vaginal pinhead elevations,[7] small submucosal nodules,[8] and a constriction involving the upper third of the vagina.[9]

The purpose of this report is to redescribe and redefine this somewhat confusing array of previously reported vaginal and cervical changes, to describe others not yet recorded, and to suggest a nomenclature by which these benign variations may be categorized for subsequent comparative compilations and study.

From the Department of Gynecology and Obstetrics, Stanford University School of Medicine.

Presented at the Forty-second Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Pebble Beach, California, October 6-11, 1975.

Reprint requests: Eugene C. Sandberg, M.D., Department of Gynecology and Obstetrics, Stanford University School of Medicine, Stanford, California 94305.

Our observations suggest that there are at least 12 distinct anatomical changes of the cervix and of the vagina. A few others have been seen but their incidence has been insufficient to establish them as unique and recurrent entities. If some of these become accepted or others are newly discovered, this categorization may need to be expanded. Hopefully, an embryologically oriented nomenclature and grouping will be developed as the mechanism of formation of these variations becomes understood.

Material

The 320 patients in the study population were all born between 1947 and 1964 and at their first visit were between the ages of 11 and 28. Their age distribution is charted in Fig. 1. All were volunteer recruits in the 28-month-old "stilbestrol study" at this institution. The mother of each certified that she had taken stilbestrol while carrying the patient in utero. Attempts to corroborate maternal memory through review of the obstetrician's prenatal record are continuing. Despite the fact that this portion of the study has not been completed and despite the fact that a distressing number of the prenatal records have been destroyed or are otherwise irretrievable, confirmatory evidence for stilbestrol exposure in utero has been obtained for 166 (51.9 per cent) of the 320 patients.

Of these patients, 244 (76.2 per cent) had not married and the remainder had; 252 (78.7 per cent) had experienced coitus and the remainder had not. The distribution of the ages in which the patients first experienced intercourse is depicted in Fig. 2.

Forty-three (13.4 per cent) of the study group have become pregnant; four are currently pregnant. The 39

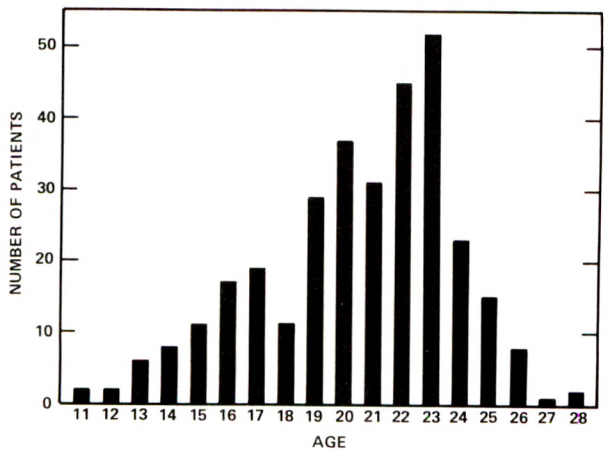


Fig. 1. Number of patients and ages when first seen in "stilbestrol study."

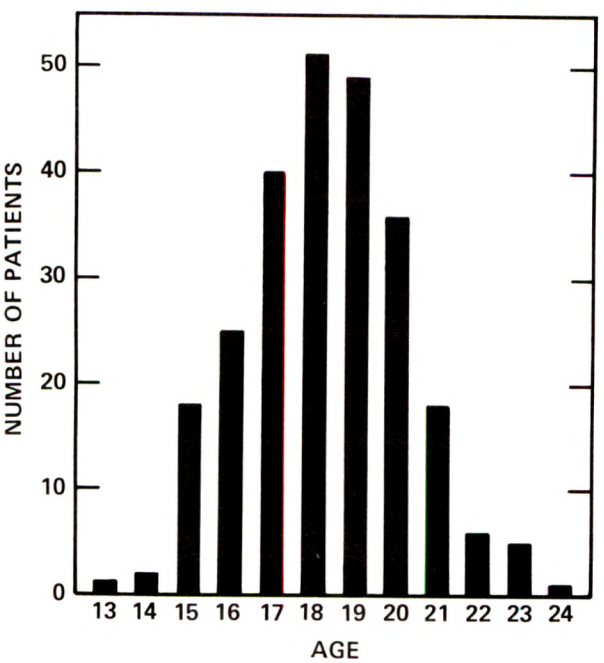


Fig. 2. Number of patients and ages at first coitus.

previously pregnant patients have had a total of 47 pregnancies. Seventeen culminated in term deliveries, three in premature deliveries, 23 in legally induced abortions, three in spontaneous abortions, and one in a tubal gestation. Only three patients complained of being unable to become pregnant. Of the 252 coitally experienced individuals, 233 (92.4 per cent) had used or were currently using oral contraceptive agents.

In addition to the 320 patients who form the basis for this report, 27 others were seen in the "stilbestrol study" but these have been excluded from current consideration. Three had previously had a total abdominal hysterectomy, two for the purpose of sterilization and one for intractable uterine bleeding. Ten patients were between the ages of 5 and 13 and were unexaminable. Fourteen were found not to have been exposed to stilbestrol in utero. None of the latter had any of the cervical or vaginal changes to be described.

Results

As previously noted in similar patient groups,[10, 11] there were no significantly recurring abnormalities noted on general or pelvic examination except in the area of the vagina and cervix. The external genitalia, uterine fundus, and adnexal organs failed to reveal any unexpected abnormalities. One patient presented with an imperforate hymen. Another patient presented with a pelvic mass and bilateral ovarian dermoid cysts were subsequently excised. An additional patient gave a history of also having had ovarian cysts excised bilaterally.

Very few patients had vulvovaginal or sexual complaints and, except for dyspareunia associated with apical vaginal narrowing, there were no symptoms which could be directly correlated with any of the changes to be described.

None of the patients had a positive Papanicolaou smear and none have developed cancer of the cervix or vagina.

Cervix. Five different changes of the cervix have been noted, all benign. These are listed descriptively in Table I and the incidence of each in the study population is noted. There were 184 patients (57.5 per cent) who revealed one or more of the following cervical changes.

Type I cervix. The pathognomonic feature of this type of cervix is the presence of a circular sulcus on the face of the exocervix. This circular depression or furrow divides the exocervix into a central disc of perioral tissue medial to the sulcus and an outer rim of exocervical tissue between the lateral border of the sulcus and the cervicovaginal junction circumferentially (Fig. 3). This is the most common type of cervical change and has been seen in over one third of the patients.

This change was first reported by Herbst and associates[1] and was described as a "concentric ridge in the cervix," as a partial "transverse vaginal septum" and as a "protruding transverse ridge of tissue (which partly or completely encircled the upper vagina" giving the appearance of a cervical collar. Pomerance[5] considered that this represented a "hood" of vaginal tissue surrounding the cervix. Stafl[12] still adheres to this interpretation but the majority of observers feel that

Table I. Types and incidence of changes seen in the cervix of 320 women exposed to stilbestrol in utero (some patients had more than one type)

Type of change	*No. of patients*	*incidence (%)*
A. Type I cervix (circular sulcus on face of exocervix)	117	36.5
B. Type II cervix (recessed area of perioral tissue)	22	6.9
C. Type III cervix (complete covering of exocervix with endocervical epithelium)	22	6.9
D. Pseudopolyp	15	4.7
E. Anterior cervical protuberance (smooth or rough)	46	14.4

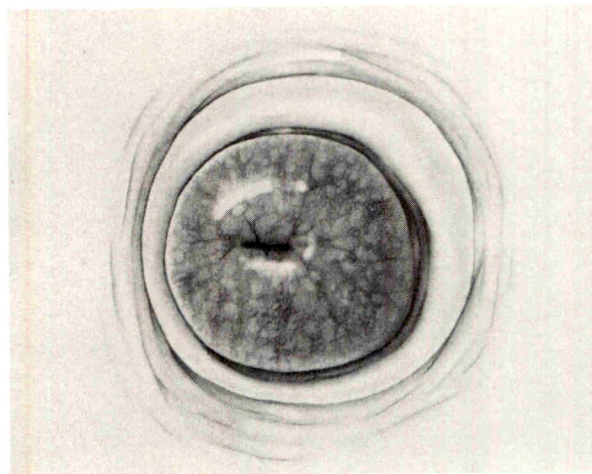


Fig. 3. Type 1 cervix (circular sulcus dividing the exocervix into two parts).

the entire unit represents the cervix. We have not had the opportunity to resolve this point by inspection of an excised specimen nor has the result of such an examination been reported. In all 117 examples in this series, however, the exterior wall of the supravaginal portion of the cervix has appeared by palpation to be a direct extension cephalad from the lateral limits of the "hood." This has served to reinforce the repetitive visual concept that this change represents simply a circular division of the exocervix.

Many minor variations of the Type I cervix are seen. The common denominator for all, however, is the perioral circular sulcus, a term for the observed anatomical change which seems more specific, less confusing, and more appropriately descriptive than "vaginal and cervical ridges."[1] The sulcus may be completely circular, as noted in Fig. 3, or only partially so. It may be prominent and obvious or only slightly more than suggestive. It may be broad or narrow, deep or shallow. Usually only a single, circular furrow is noted but occasionally multiple, fernlike channels may be noted arranged in the same circular fashion.

The perioral disc of tissue within the confines of the sulcus is usually mildly convex and only rarely is this tissue not elevated above the level of the outside rim of exocervical tissue. Occasionally it is conically convex like the penile glans and, on some occasions, is singularly protuberant and almost barrel-shaped. An external os is invariably visible at or near its center. Examples of this latter variation have previously been referred to as "pseudopolyps."[1, 4] It is probably better, however, for this term to be reserved for a similar but more distinctive lesion to be described shortly.

The rim of exocervical tissue peripheral to the sulcus usually is broader anteriorly than posteriorly and in many instances is so narrow posteriorly that a very deliberate exposition of this area is required to confirm its existence.

Most commonly the perioral disc of tissue within the sulcus is covered by columnar epithelium of the endocervical variety which gives the entire perioral area the characteristic appearance of cervical "erosion" or ectropion. Small Nabothian cysts may occasionally be noted. The red, granular, eroded appearance is the result of the viewer's visualization of the capillary bed through the transparent, and consequently invisible, single layer of mucus-producing columnar cells which form the surface. The exocervical rim most commonly is covered by squamous epithelium. Every conceivable combination of these epithelia has been seen in these areas, however, including complete squamous epithelialization of the tissue medial to sulcus associated with complete columnar epithelialization of the exocervical rim. Squamous metaplastic changes in the epithelial surface have been noted over the course of multiple examinations in a few patients but the sulcus has never been seen to change in its depth or breadth or to become filled-in at any point. The Type I cervix appears to be anatomically stable.

Type II cervix. The characteristic feature of the Type II cervix is the presence of a recessed area of tissue about the deeply placed external os (Fig. 4). The remainder of the exocervix exhibits its normal convexity and there is no evidence of a circular sulcus. The recessed perioral area is conical, may be 0.5 to 2 cm. in diameter, is generally shallow but obvious, and gives a craterous appearance to the tip of the cervix. The external os is located at its base and is usually centrally placed. This coned-out–appearing, perioral area may have steep or gently sloping sides and may have either

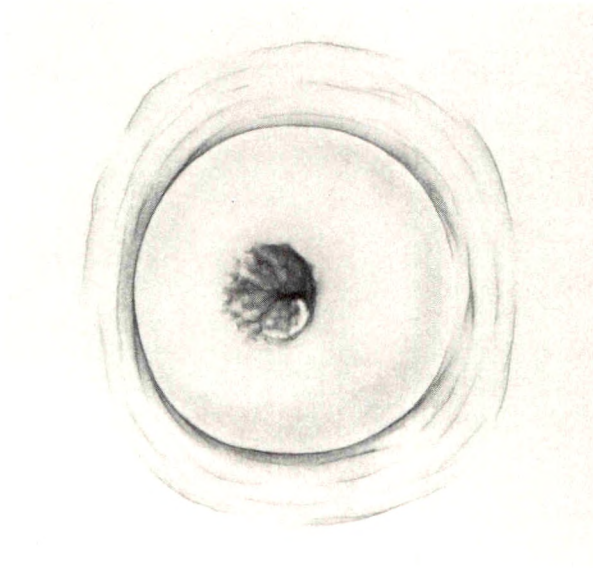


Fig. 4. Type II cervix (recessed area of perioral tissue).

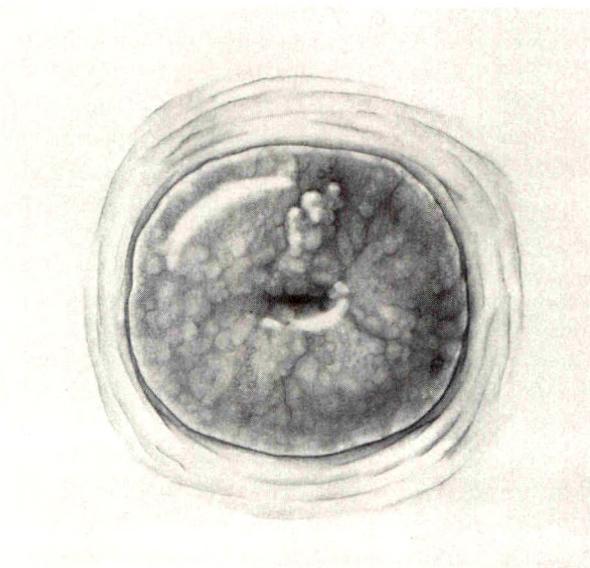


Fig. 5. Type III cervix (complete covering of the exocervix with endocervical epithelium).

a smoothly circular or a slightly irregular and eccentric rim. In the classical example, it seems as though one is peering into the depth of a widely dilated endocervical canal. Pomerance[5] described this an an "endocervical lesion."

The recessed area is most commonly lined by columnar epithelium which gives the perioral area the red, raw appearance of cervical ectropion. The remainder of the exocervix is usually covered by squamous epithelium. Different combinations of these epithelia have been seen on the Type II cervix,

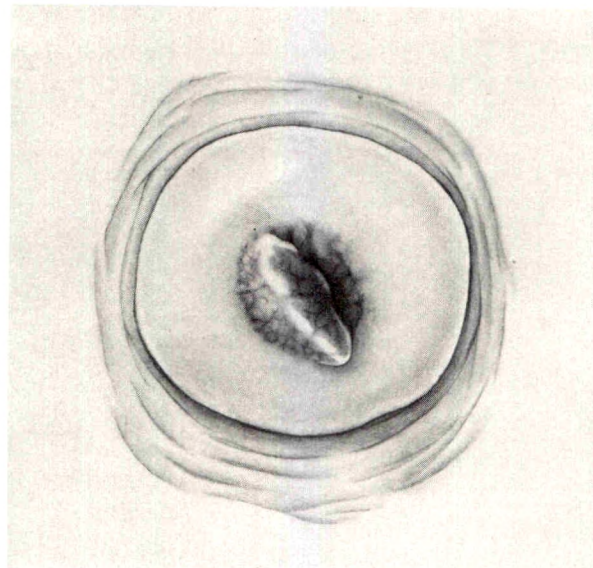


Fig. 6. Pseudopolyp of cervix.

however, including instances in which both the recessed perioral area and the remainder of the exocervix were covered by columnar epithelium as well as instances in which both were covered by squamous epithelium. While squamous metaplasia of varying degree has been noted to occur both inside and outside the recessed area, neither a deepening, widening nor a filling-in of the recessed area has been observed. The Type II cervix appears to be anatomically stable.

Type III cervix. The essential feature of the Type III cervix is the presence of columnar epithelium of the endocervical variety over the entire face of the exocervix from the external os to the cervicovaginal junction circumferentially (Fig. 5). The exocervix in its entirety has the red, raw appearance of cervical ectropion and commonly exhibits on its surface a moderately thick layer of colorless, light-reflecting mucin produced by the surface-covering cells. There is no evidence of a circular sulcus or a perioral recessed area.

The exocervical surface of the Type III cervix may be smoothly convex or may be bubbly, bumpy, and highly irregular with localized outgrowths and cystic dilatations of the misplaced columnar epithelium. Squamous metaplasia of varying degree has been noted to occur but never to the point of total conversion to mature squamous epithelium. The longest duration of observation, however, has only been 2 years. There has been no other evidence of change. The Type III cervix appears to be anatomically stable.

Pseudopolyp. The pseudopolyp is a localized hypertrophy of endocervical tissue which is located at the

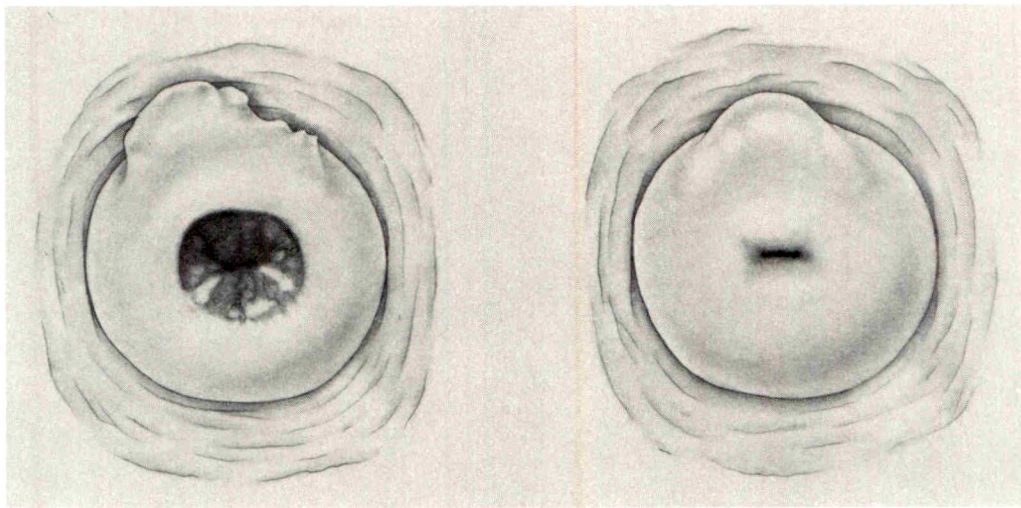


Fig. 7. Anterior cervical protuberances. Rough, pictured with Type II cervix at left; smooth, pictured with normal cervix at right.

external os, has a broad base and is almost invariably covered by columnar epithelium (Fig. 6). It is usually solitary, but may appear in pairs. It is generally round if small and eccentrically bulbous if large. It may range in dimension from 5 mm. to several centimeters. Pseudopolyps do not have the thin stalk that is seen with true polyps of the endocervix and, because of their broad base, will bleed vigorously if detachment or disruption is attempted. All of those noted in this study have been completely asymptomatic and have failed to exhibit any structural or surface epithelial changes at subsequent examinations. All were noted at the initial examination and none have developed while the patients were under observation. The pseudopolyp appears to be anatomically stable.

The term "pseudopolyp" was originally used by Shane and Perlmutter[4] and subsequently by Herbst and associates[1] to describe a uniformly protuberant cylinder of perioral cervical tissue through the center of which ran the endocervical canal. A circular sulcus was present about its base, separating it from an outer rim of additional exocervical tissue. Their photographs are excellent examples of a minor variation of that which has been termed a Type I cervix in this publication. It is suggested that the term pseudopolyp be reserved hereafter for broad based, localized excrescences from the wall of the endocervix at or above the level of the external os and that it not be used to describe cervical tissue which embraces or encircles the endocervical canal.

Anterior cervical protuberance. Protuberances of different sizes which have two basic forms are noted on the anterior portion of the exocervix. Many of these

Table II. Types and incidence of changes seen in the vagina of 320 women exposed to stilbestrol in utero

Type of change	*No. of patients*	*Incidence (%)*
A. Surface adenosis	77	24.1
B. Cystic adenosis	58	18.1
C. Mucosal membrane	12	3.7
D. Corolla-like mucosal elevation	2	0.6
E. Fibrous bands	9	2.8
F. Apical narrowing	12	3.7
G. Forniceal obliteration	3	0.9

protuberances have a somewhat jagged, lumpy, and irregular form and are consistent with the cervical "cock's-comb–like lesion" described by Pomerance.[5] Others, however, have a smooth surface and give the appearance of a smoothly rounded, conical snout or a convex, cystlike mount (Fig. 7). The smooth form is five times more prevalent than the rough form.

Both forms vary in diameter from 5 to 15 mm. and are usually broader transversely than they are anteroposteriorly. They usually appear singly but may occur in pairs. In the latter circumstance, both may be smooth, both may be rough or one of each may be present.

The epithelium covering the smooth protuberance is almost invariably squamous in nature whereas that overlying the rough protuberance may be columnar, squamous or a metaplastic combination.

The protuberances may appear on any variety of cervix. On the Type I cervix they have been seen medial to the sulcus, peripheral to the sulcus, or

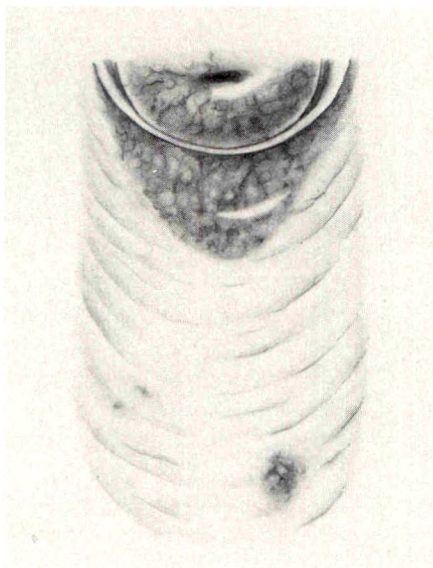


Fig. 8. Surface adenosis in four different areas on the posterior vaginal wall, pictured with Type I cervix.

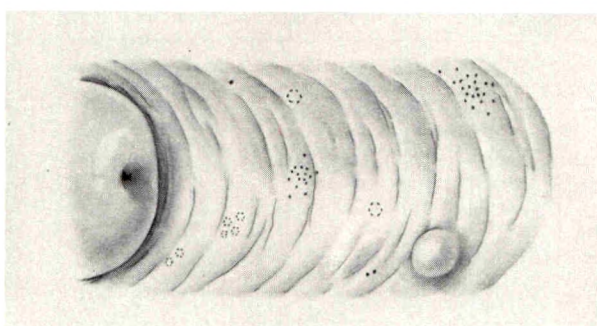


Fig. 9. Cystic adenosis on the left lateral vaginal wall, pictured with normal cervix. The largest cyst is clinically visible. The remainder are detectable only by palpation.

bridging the sulcus. The majority appear at the high point on the cervical crown, above the cervicovaginal junction and well away from the external os. Cervical protuberances have been seen in 46 patients in this study and in every instance have been located on the anterior exocervix between 10 and 2 o'clock. None have been seen, nor described in the literature, in any other area of the exocervix. Consequently, it seems reasonable to designate these changes as anterior cervical protuberances with a subclassification of smooth or rough. The term "cock's comb," though appropriate for some, is inappropriate for all.

None of these protuberances has been noted to change in any manner. Like all of the cervical changes described, they appear to be anatomically stable.

Vagina. A greater array of vaginal changes than cervical changes has been noted. Vaginal changes, however, occur in a smaller percentage of patients (37.8 per cent), are less obvious than those on the cervix, and are distinctly more difficult to discover and to interpret. The vaginal changes are listed in Table II and the frequency of their occurrence in the study population is noted.

Surface adenosis. In a previous publication in which the existing forms of vaginal adenosis were described,[13] this form was labeled "effluent adenosis." The term surface adenosis is simpler, more descriptive, avoids the implication that the developmental process is understood, and will be used hereafter. The most common vaginal abnormality seen is surface adenosis, the simple replacement of vaginal squamous epithelium with a single layer of mucus-producing columnar cells histologically and histochemically identical with those normally present in the endocervix. Surface adenosis is usually easy to identify with the naked eye and has the typical appearance of cervical ectropion displaced onto the vagina (Fig. 8). As with cervical ectropion, the transparency of the single layer of columnar cells allows the examiner to visualize the capillary bed of the subcutaneous tissue as though no epithelium existed. The lack of bleeding, even with moderate frictional trauma, and the frequent existence of a covering sheen of crystal-clear mucus clinically confirm the presence of an endocervical columnar cell surface. Squamous metaplasia is common in these areas, however, and as it progresses the epithelium becomes multilayered, the capillary bed becomes obscured, the surface begins to take on the characteristics of squamous epithelium, and the existence of surface adenosis becomes less apparent to the naked eye. Under this circumstance, colposcopy may become useful in identifying and following this change inasmuch as metaplastic epithelium and remnants of surface adenosis, if present, can be seen with this instrument. Colposcopy was not used in this study, however, and all observations were made with the unaided eye.

Surface adenosis in patients exposed to stilbestrol in utero most commonly appears in the anterior and posterior fornix and most commonly appears in a triangular form with its base at the cervicovaginal junction. Usually, the involved area is small (e.g., 15 by 15 mm.) but occasionally may involve as much as one third or one half of the vaginal mucosa in the anterior and/or posterior midline. The lateral walls and the inferior two thirds of the vagina are occasionally involved but far less frequently than the anterior and posterior walls in the upper one third.

In most instances the red, raw-appearing areas of surface adenosis have discrete borders and are readily

visualizable. Occasionally they may be seen simply as red dots, 1 mm. or more in diameter, or the involved area of the vaginal mucosa may have a red, dappled effect due to the presence of reddish streaks or smudge-like splotches of varying width and size. These areas often have indefinite margins and lack any patterned relationship to each other. Varying degrees of squamous metaplasia may be seen in these areas at any single examination. At successive examinations a progression of squamous metaplasia may be noted, as previously described.

In at least nine patients, areas of adenosis were observed to disappear, having undergone complete metaplastic transition to squamous epithelium. None of the patients developed an abnormality of metaplasia adequate to produce an abnormal Papanicolaou smear. In the majority of patients the adenosis was noted to be stable and the process of metaplasia was not evident.

In at least 27 patients it was felt that new areas of surface adenosis developed or evolved de novo between examinations. This is recognized as being opposed to current theory regarding the immutability of native squamous epithelium and the natural history of squamous metaplasia, at least as far as the epithelium of the exocervix is concerned. It is also recognized as being exceptionally difficult to prove. Nonetheless, the observation was made repeatedly and warrants evaluation.

Cystic adenosis. The second most common vaginal abnormality detected in these patients is cystic vaginal adenosis, the presence in the vaginal submucosa of mucin-filled, cystic spaces lined by endocervical epithelium (Fig. 9). Most commonly the cysts range from 1 to 5 mm. in diameter, do not visually distort the vaginal wall and are not visually detectable. They are usually firm, however, and can be found by palpation if the examiner is very attentive and thoroughly palpates every portion of the vaginal mucosa. On the other hand, those that are larger than 1 cm. in diameter are usually easily seen if a specific effort at visualization of the entire vaginal mucosa is undertaken. They are often impossible to detect by palpation, however, because their texture is soft and not substantially different from that of the vaginal wall.

The smaller cysts frequently appear singly and feel like a grain of sand or a single BB within the mucosa. On occasion, however, they have been so numerous, tiny, and well localized that they have given a grainy, sandpaper-like quality to a sizable area of the vaginal mucosa. As previously implied, the majority will go undetected unless a very meticulous palpatory examination of the vaginal mucosa is undertaken. Inasmuch as it is our anticipation that small nodulations in the vaginal wall will ultimately be found to be the earliest manifestation of the majority of clear-cell adenocarcinomas of the vagina, this type of meticulous palpation of the vaginal mucosa is considered to be a vital part of each examination.

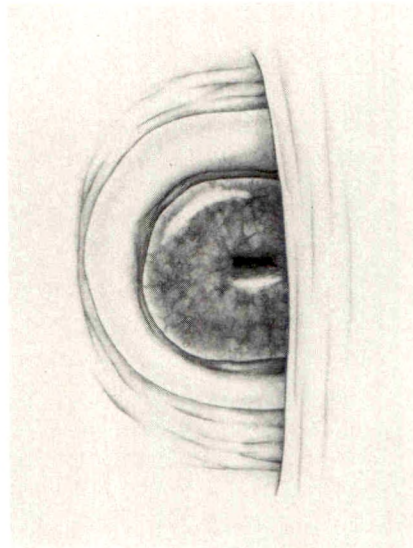


Fig. 10. Vaginal mucosal membrane, pictured with Type I cervix.

Cystic adenosis has frequently been noted to develop in the interval between examinations but rarely have any of the cysts shown advancement in size subsequent to their initial detection. On occasion they have been noted to spontaneously disappear. In all 58 patients in whom cystic adenosis has been detected, the cysts have been asymptomatic.

Mucosal membrane. The mucosal membrane is a narrow, veil-like strip of vaginal mucosa which covers and totally obscures the left fornix (Fig. 10). This thin membrane appears to be redundant lateral vaginal mucosa which bridges from the left anterior fornix at 1 o'clock to the left posterior fornix at 5 o'clock. It originates and inserts approximately 1 cm. distal to the cervicovaginal junction. The transverse width of the membrane is variable. In some patients it covers only the left fornix while in others it covers both the left fornix and a greater or lesser portion of the left half of the exocervix.

Because of its apparent tenseness on distension of the upper vagina with a speculum and because of its proximity to the cervix, the membrane prevents visualization of the left fornix. The fornix seems to be fully developed, however, inasmuch as a dimensionally consistent space may be delineated behind the membrane by the insertion of a right-angled probe. The right fornix has invariably been expansive and easy to

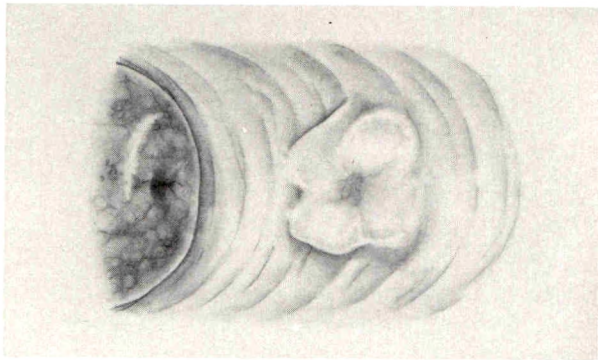


Fig. 11. Corolla-like mucosal elevation on the left lateral vaginal wall, pictured with Type III cervix.

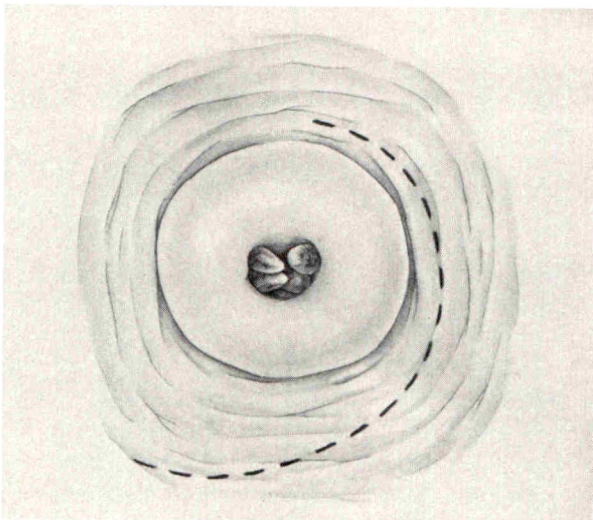


Fig. 12. Vaginal fibrous band, pictured with normal cervix and with true polyps within external os. Band is beneath vaginal mucosa and detectable only by palpation.

examine. It gives the impression of being compensatorily enlarged even in the four individuals in this group who have not yet experienced intercourse. In most patients exhibiting a mucosal membrane, the cervix is centrally located in the pelvis but in a few the cervix is displaced to the left of midline and associated with a thickened and shortened cardinal ligament.

The mucosal membrane is essentially impossible to detect by palpation because it has the same consistency and pliability as the remainder of the vaginal mucosa. In one patient, however, it was readily detectable in that a palpable 1 cm. diameter cyst was incorporated in the midportion of the membrane. Surface adenosis, however, has never been noted on the distal surface of this membrane. None of the mucosal membranes has changed in any regard while under observation. The mucosal membrane appears to be anatomically stable.

The most inexplicable finding associated with these membranes is their unilaterality. All 12 have been situated on the left and have been absolutely identical in their geographic location. None has been seen anteriorly, posteriorly, on the right or with any other geographic bridging than from 1 to 5 o'clock described. On this as well as other bases, it seems inappropriate to consider them, even momentarily, as incomplete vaginal septa. They appear to be even more unusual than that terminology would imply.

Corolla-like mucosal elevation. Another unique and distinctive type of vaginal mucosal change is the multipetaled corolla-like elevation of the vaginal mucosa (Fig. 11). This is a discrete, sharply demarcated, 1 to 2 cm. broad, festooned, flower-like lesion which is elevated approximately 0.5 cm. above the surrounding vaginal mucosa. To date, this has been seen in only two patients and in each it was located in the left fornix with its cephalic border 1 cm. distal to the cervicovaginal junction. Because of the unique appearance, because of the lack of previous detection and description and because of the identicalness in appearance and anatomic location of the lesion in two patients in this select group, it seems reasonable to anticipate that this is a separate and specific entity developed in association with stilbestrol exposure in utero. It is also probable that its incidence is greater than noted here inasmuch as the lesion was overlooked in both patients until the second or third examination and was detected in the second patient only 3 weeks after it was initially recognized in the first.

The corolla-like lesions were totally covered with mature squamous epithelium except for the presence in one of a 5 mm. diameter center which was red and raw-appearing as though covered with columnar epithelium. Texturally, the lesions were identical with the surrounding vaginal epithelium and, consequently, were not identifiably distinct on palpation.

The observation periods have been too short since discovery of these changes to allow any statement regarding their stability. Their appearance, however, would suggest lifetime durability both anatomically and histologically.

Fibrous band. A fibrous band is a thin wirelike strip of fibrous tissue which has been found to completely or partially encircle the vaginal barrel in nine patients in this study (Fig. 12). In all instances it has been solitary, been present in the upper one third of the vagina and has not been detectable on inspection. It seems to lie immediately beneath the vaginal mucosa but there is no aberration or modification of the overlying mucosa that has been seen to suggest its existence. It is detectable on palpation but only by widely spreading

the two examining fingers while probing deeply within the vagina. The normal pliability and distensibility of the vaginal mucosa is noted in all areas except at the point of the submucosal fibrous band. At this location, a tense, unyielding, wire-like constriction prevents the normal stretching.

Totally encircling fibrous bands have been found but these are less common than those which only partially encircle the vagina. The incompletely encircling bands may arc anteroposteriorly (12 to 3 to 6 o'clock) or transversely (3 to 6 to 9 o'clock). Not infrequently one end of the band is noted to be more distally removed from the cervicovaginal junction than the other.

Three of the nine patients with a fibrous vaginal band also demonstrated apical vaginal narrowing (to be described). Only one of the patients experienced dyspareunia. None experienced other pelvic symptoms. No spontaneous change has been seen to occur in any of these structures. The fibrous band appears to be anatomically stable.

Apical narrowing. Apical narrowing is a conical constriction of the upper one third of the vagina (Fig. 13) and has been seen in a dozen patients in this study. Occasionally it is associated with a small cervix (less than 1.5 cm. in diameter) and with shallow or nonexistent fornices. It is not easily detected by inspection alone and is most frequently noted when attempting to distend the deep vaginal mucosa by forcibly separating the too examining fingers. The mucosa distal to the area of narrowing is pliable and demonstrates normal distensibility while that within the area of apical narrowing is more tense and only minimally distensible.

It is readily understandable why four of the 10 patients with this vaginal change who have experienced intercourse noted dyspareunia on deep penetration during their early coital activity. In all cases, the dyspareunia disappeared with continued intromission. No other symptoms have been noted. No physical change has been seen in the area of apical narrowing at subsequent examinations and the abnormality appears to be anatomically stable.

Forniceal obliteration. Absence or obliteration of a single vaginal fornix (Fig. 14) has been seen in three patients in this study. In each situation the vaginal mucosa in that area tented directly onto the crown of the exocervix well above the level of the cervicovaginal junction which was readily visible in the adjacent fornices. This solid, mucosal, bridgelike obliteration was noted anteriorly in one patient, on the right in another, and on the left in a third. The mucosa revealed no abnormalities and the cervix was apparently uninfluenced either anatomically or histologically by this vaginal mucosal bridging. The patients were asymptomatic and did not experience dyspareunia.

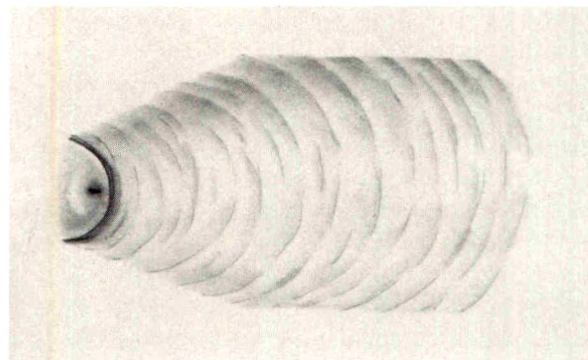


Fig. 13. Apical narrowing of the upper one third of the vagina, pictured with normal, though small, cervix.

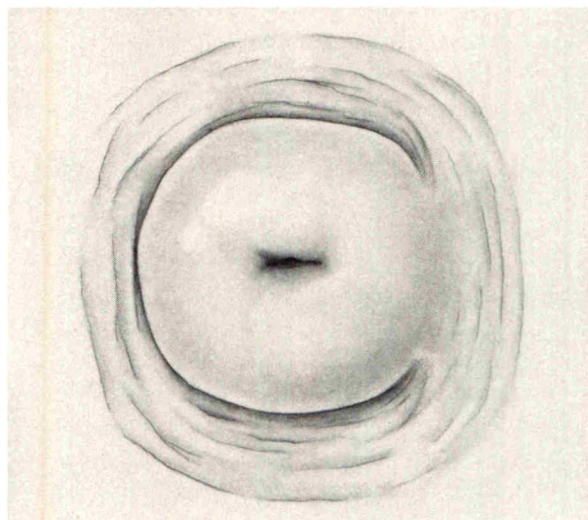


Fig. 14. Obliteration of the left vaginal fornix, pictured with normal cervix.

A possible variant of this change was seen in a fourth patient in whom a semilunar, 2 to 3 mm. wide strip of squamous-covered tissue was noted to bridge across (but not obliterate) the anterior fornix. It stretched from an attachment on the face of the exocervix at 2 o'clock 1 cm. from the external os to the vaginal mucosa in the right fornix at 10 o'clock 1 cm. distal to the cervicovaginal junction.

Miscellaneous changes. Benign changes of the cervix and vagina other than those described above have also been noted. These do not currently seem to warrant classificational recognition, however, because they are insufficiently unique, have been difficult to define and evaluate, or have appeared too infrequently to assume that they represent a characteristic of this patient population. Enumeration of these seems desir-

able, however, for completeness and for comparison with the observations of others working with similarly exposed patients. If any of these miscellaneous changes are seen frequently by others, the categorization should be extended to allow their inclusion.

Unusual cervical size. Although no tabulations were kept and a control population was not utilized, the incidence of cervices of unusual size intuitively seemed to be greater than anticipated in a population of young and largely nonparous women. Cervices of unusual size would include those less than 1.5 cm. in diameter, more than 3 cm. in diameter, and/or less than 1 cm. in length.

Unusual diameter and form of external os. A seemingly common finding was a parous-appearing os in a nulliparous patient. A transversely elliptical, "fish-mouth-like" external os and a rather widely gaping, circularly distended external os were both seen more often than anticipated but their incidence was not tabulated.

In one nulliparous patient, the external os formed the posterior end of a deep, narrow trough that ran from the central portion of the exocervix to the cervicovaginal junction in the anterior midline (12 o'clock), splitting the exocervix into a U-shaped organ. The cervix of her identical twin, who from a comparative standpoint unfortunately had had two term vaginal deliveries, had the more typical appearance of bilateral, unapproximated, transverse lacerations extending from the external os to the cervicovaginal junction at 3 and 9 o'clock. There was no evidence of the vertically oriented trough seen in her twin.

Partial transverse vaginal septum. In the initial report of benign cervical and vaginal changes seen in patients exposed to stilbestrol in utero, Herbst and associates[1] described one patient in whom a transverse vaginal septum with a narrow central opening "partially obliterated the upper third of the vagina." Incision of the septum was required in order to visualize the cervix. Other equally distinctive descriptions of partial transverse vaginal septa have not appeared in subsequent reports concerning similarly exposed patients. It is possible that this was simply a random finding. However, we have seen one patient who exhibited a loose, redundant fold of vaginal mucosa arcing from 3 to 6 to 9 o'clock across the posterior midline at the junction of the upper and middle thirds of the vagina. This fold rose approximately 1 cm. above the level of the adjacent vaginal mucosa but no significant clinical constriction of the vaginal lumen was apparent. There was no history of dyspareunia. This is the only item seen in any of these patients which could reasonably be interpreted as a partial transverse vaginal septum.

Pericervical fibrous collar. An occasional patient, usually one with a Type 1 cervix, seemed to exhibit a submucosally placed, supravaginal ring of fibrous tissue about the cervix midway between the internal and external os. Most commonly, the ring felt to be about 0.5 to 1 cm. thick, was palpable but not visible, and was essentially impossible to distinguish from the ring of exocervical tissue peripheral to the sulcus in the Type 1 cervix. We have not been able to establish this as a specific entity inasmuch as we have not had the opportunity to evaluate an adequate number of patients with normal cervices who additionally exhibited this change nor have we had the opportunity to study an excised uterus clinically presumed to bear this abnormality.

Comment

It is currently well recognized that human females exposed to stilbestrol in utero have an exaggerated incidence of clear-cell adenocarcinoma of the cervix and vagina. It has also been demonstrated that females so exposed who do not have a cancerous process in the genital tract nonetheless have characteristic and essentially pathognomonic benign changes in the cervical and vaginal tissues. That the changes are multiple in nature and that over two thirds of the exposed female population exhibit one or more of these changes is not well known. That these changes may be readily detected by meticulous visual and palpatory examination which does not require special instruments or stains is of significant interest.

The method of development of the majority of the cervical and vaginal changes described is not obvious from our current state of knowledge. In order to explain the observed developmental variations, more explicit information will have to be obtained regarding the embryologic formation of the upper vagina and cervix, the normal postnatal development of these tissues, and the teratogenic influence of the stilbene molecule on both their embryologic and postnatal differentiation.

It is likely that the incidence figures for the various changes described in this report represent minimal percentages of occurrence rather than either mean or maximal figures. The changes described here have been discovered as the study has progressed. A number of the patients have failed to return for repeat observation and initial interpretations and discoveries have had to suffice. Despite the fact that the majority of these changes were recognized during the examination of approximately the first 50 patients, recognition has improved with familiarity and occasional new and apparently previously overlooked aberrations continue

to be seen. As previously mentioned, the most recent of these, the corolla-like mucosal elevation, was first discovered in a previously examined patient 2 years after the study was initiated. This suggests that other currently unrecognized changes may also suddenly become appreciated and that meticulous visual and palpatory scrutiny of the *entire* vagina and cervix must be undertaken at each visit. A checklist approach is suggested using the changes listed here and including both a cervical and a vaginal category termed "Other?"

It is of interest and possibly of importance to recognize that the cervix and the vagina (and possibly the cervical support ligaments) have been the only organs shown to bear these benign imprints of embryologic stilbestrol exposure. In this regard it is significant that the unusual cancers to which these patients are heir are apparently limited to these same organs.

While we have not had the opportunity to fully digest the data, it appears that not every cervix or vagina exposed to stilbestrol at the same embryologic moment receives the same imprint. Also, it is evident that this exposure, with or without the residue of a physical imprint, does not invariably lead to the development of clear-cell adenocarcinoma. Whether any of the changes described here bode ill for any of the patients is unknown but none has been seen to progress or deleteriously change during observation periods ranging from a few months to 2 years.

We have not been able to determine the effect of pregnancy on the described changes or the effect of the changes on pregnancy. Relatively few of the patients are parous and only one patient progressed through pregnancy during the study. Her prenatal course, labor, and vaginal delivery were totally normal. Her Type 1 cervix remained unchanged. None of the patients with a mucosal membrane, corolla-like mucosal elevation, fibrous band, apical narrowing, or forniceal obliteration have yet experienced full term gestation.

Also we have been unable to determine if reproductive ability has been influenced in any manner in this patient population. No glaring proficiency or deficiency has been noted thus far. As previously mentioned, the majority of the patients do not yet desire pregnancy and half of those in whom it has occurred have voluntarily rejected it via induced abortion.

In this regard, it should be noted that over 90 per cent of the coitally experienced patients in the study have had some degree of exposure to orally ingested contraceptive agents, many continuously for years. We have not observed any progression or other variation in any of the described changes following the initiation or the discontinuation of the use of oral contraceptive medications. Nor do we have reason to believe that any of the changes recorded here appeared as a result of oral contraceptive use. To date, the experience with this group of patients fails to suggest any contraindication to the use of birth control pills in women exposed to stilbestrol in utero. Conversely, no evidence has appeared in this group to suggest that a beneficial effect on these changes will accrue as a result of oral contraceptive use.

Over two thirds (67.2 per cent) of the study group exhibited one or more of the cervical or vaginal changes described. If we accept the tenet that these changes are rarely seen in patients unexposed to stilbestrol in utero, this implies that approximately two thirds of the females at risk, many unaware of their exposure to stilbestrol in utero and many unaware of their accentuated potential for the development of clear-cell adenocarcinoma, could be identified simply by the findings at pelvic examination. While a simple query of every female patient under 30 years of age regarding known exposure to stilbestrol in utero should currently be standard practice, the additional awareness of these physical indications of such exposure should prove to be beneficial to patient and gynecologist alike.

Drawings were done by Nancy J. Lawton.

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Discussion

DR. RICHARD A. BASHORE, Los Angeles, California. In 1965 Sandberg and colleagues[1] published a report concerning four cases of vaginal adenosis, one of which was associated with adenocarcinoma of the vagina. Although at that time he did not appreciate the association between intrauterine exposure to stilbestrol and subsequent development of this lesion, the last paragraph of his paper indicates that Sandberg[2] may have been the first to suggest an increase in the incidence of vaginal adenosis. I quote: "It is concluded that neglect of this subject in American texts and journals is unwarranted and that if the entity was sufficiently popularized, its apparent incidence would rise abruptly." Again in 1967, before a meeting of this Society, Dr. Sandberg reported the presence of occult vaginal adenosis in nine of 22 vaginas of postpubertal women studied extensively at autopsy.

In the paper presented today, Dr. Sandberg has suggested a logical nomenclature for a variety of benign changes in the vaginal and cervical areas which may be associated with exposure to stilbestrol in utero. This classification of benign changes will prove most useful to those who are evaluating large numbers of stilbestrol-exposed patients as a means of standardizing comparison of these abnormalities. The precise descriptions should also be helpful to gynecologists and others who may examine possibly exposed patients only occasionally. At least the examiner will be forewarned as to the types of alterations which may occur, their gross appearance, and their anatomic location. Elimination of such terms as "cocks comb" and "strawberry" cervix, as Dr. Sandberg suggests, should also be advantageous in achieving a more uniform depiction of these abnormalities.

Although Dr. Sandberg did not make a specific recommendation as such, it may be inferred from the paper that any informed clinician could satisfactorily screen exposed patients. An inquiry of each patient less than 30 years of age as to possible exposure to stilbestrol, coupled with a meticulous examination of the cervix and vagina, should permit detection of these abnormalities in the vast majority of cases.

With regard to prognosis, it is reassuring to hear that the majority of cervical and vaginal changes described remained anatomically stable during the follow-up period. This is especially pertinent in that approximately 90 per cent of patients in the series were exposed to oral contraceptive agents during the course of the study.

Of the benign changes described by Dr. Sandberg, the one which will no doubt evoke most discussion is vaginal adenosis. As I interpret the methodology, visualization and palpation of the vagina were the only techniques utilized in detecting vaginal adenosis. I would suggest that Schiller's staining of the vagina is an important diagnostic aid in identifying areas of squamous metaplasia or dysplasia which may obscure underlying adenosis. Many would also take exception to the statement that 27 patients developed vaginal adenosis de novo during the course of the study. It may be that these changes were not detected on prior examinations for the reason previously stated.

With regard to detection of a vaginal adenosis, I would like to present the data compiled by Drs. Lagasse, Lebherz, and Watring[3] from the UCLA Stilbestrol Clinic. This study concerns an evaluation of 200 women with possible prenatal exposure to stilbestrol. In the UCLA study three methods were compared as to their accuracy in predicting the presence or absence of vaginal adenosis; clinical evaluation, biopsy of the anterior vaginal wall, and vaginal scraping with a wooden spatula covered at the tip with a strip of Velcro. The advantage of Velcro scraping is the ability to sample somewhat deeper layers of vaginal cells than could be obtained with customary vaginal smear techniques. The investigators also strongly recommend staining with Schiller's solution as an aid in identification of abnormal areas. The relative accuracy of the three methods is depicted in Table I. It was concluded that a combination of the three techniques could improve the over-all accuracy in determining the presence or absence of vaginal adenosis.

Other questions may be raised concerning these interesting lesions. What is the relationship between vaginal adenosis and the development of clear-cell adenocarcinoma of the vagina? What is the risk of development of vaginal squamous cancer in dysplastic epithelium overlying areas of adenosis? At a recent meeting of the American Cancer Society Division of Gynecologic Oncology, Dr. Ulfelder[4] stated that the peak age incidence for development of clear-cell adenocarcinoma seemed to be remaining at around age 19 to 20. One reasonable interpretation of this statistic would be that as all stilbestrol-exposed women passed beyond their 20's, the increased risk of de-

Table I. Comparison of accuracy of histology, clinical findings, and cytologic evaluation in 200 patients studied for possible vaginal adenosis

	Predicted the presence or absence of vaginal adenosis	*(%)*
Histology	179	89.5
Clinical evaluation	154*	90.6
Cytologic evaluation	185	92.5

*Corrected for cervical adenosis patients.

velopment of clear-cell adenocarcinoma should decrease significantly.

In his initial abstract concerning the paper presented today, Dr. Sandberg indicated that he had intended to correlate the timing and duration of exposure to stilbestrol with subsequent vaginal and cervical abnormalities. We would all encourage Dr. Sandberg to continue this pursuit. The information obtained could not only contribute to a better understanding of the pathogenesis of the lesions described today but might be helpful in an earlier recognition of the possible effects of other drugs on fetal development.

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DR. SANDBERG (Closing). My first remark relates to the potential association of vaginal adenosis and clear-cell adenocarcinoma. I think all of you are aware of the repeated speculation that the ectopic endocervical cell of vaginal adenosis is the cell of origin of clear-cell adenocarcinoma. I think it must be kept in mind, however, that a histologic transition from benign endocervical cells to clear-cell adenocarcinoma cells has not been seen in any of the 170 vaginal and cervical clear-cell adenocarcinomas reported in the national registry of such tumors.

This obviously does not mean that vaginal adenosis cannot be the progenitor of clear-cell adenocarcinoma. But, if it is, it seems odd that this histologic transition has not yet been demonstrated. This is especially true when one considers the fact that, in those cases reported in the Registry in which there has been enough surrounding normal tissue excised to give good histologic exposition, benign adenosis has been present in 92 per cent. If the adenosis cell is the progenitor, one would intuitively anticipate from this number of cases that some pathologist ought to have been able to demonstrate histologic transition.

Second, I would like to clarify one item of Dr. Bashore's discussion. He stated that in the first article we published relative to adenosis we described four cases, one of which was a clear-cell adenocarcinoma. That is not quite accurate. It is true that one of the patients did have a vaginal carcinoma but the important aspect, as far as I am concerned, is that that carcinoma histologically was the standard variety of endocervical adenocarcinoma and was not clear-cell adenocarcinoma. Additionally, in that case we were able to demonstrate a clear-cut histologic transition from the benign, ectopic endocervical cells to the malignant, garden variety of adenocarcinoma cells.

As to the potential for the development of primary squamous carcinoma during the metaplastic transition of surface vaginal adenosis to squamous epithelium, I can only say that this is one of several premature speculations that are being made in this subject area. Inasmuch as there are no supporting data or evidence available at present, I would prefer to acknowledge existence of the speculation but reserve comment for a time when more information is available.

As to the desirability of the utilization of an iodine stain, it is quite true that this technique might be of benefit as another of the screening methods. We started to utilize this approach only 6 months ago and I have not attempted to correlate it and to see whether or not abnormal staining of the vaginal wall occurs in any patients who do not have any of the other changes that I have just described. Consequently, I do not know if it will extend the current observations or not.

Surface scraping and biopsies have been utilized in the attempt to diagnose surface adenosis. The colposcope has been used as well. There has been a great deal of attention applied to methods for the diagnosis of vaginal surface adenosis. While I think it is reasonable and desirable to attempt to understand and to make observations relative to anything which may be present which is peculiar or unusual, I am currently uncertain as to the absolute benefit the patient may derive from such detection. On the basis of current information, vaginal adenosis does not require therapy.

Stage I carcinoma of the uterine cervix in patients under 40 years of age

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A retrospective analysis was made of 94 patients, 39 years of age or younger, who were treated for Stage I carcinoma of the uterine cervix from 1942 through 1972 at the Los Angeles Tumor Institute and the Southern California Cancer Center. Comparisons were made between the frequency of Stage I and other stages of carcinoma of the uterine cervix, as well as the frequency of Stage I carcinoma in young and older individuals. Survival rates for the younger group were compared to those for the same stage of disease for all ages of patients. There is discussion of the treatment modalities used in light of recommendations for future plans of therapy for these young patients. Tumor recurrences are discussed, with special reference to 43 patients who survived over 10 years. Eight of these patients were found to show new or recurrent tumors after this period of time. The importance of careful, long-term follow-up and early secondary treatment for recurrent lesions is emphasized, since subsequent radical surgery may salvage a number of these individuals.

THIS DISCUSSION concerns the proper management of young individuals who have early invasive carcinoma of the uterine cervix. In such young patients, with presumably controllable lesions, one would assume a relatively long life span. Primary radical surgery, with ovarian preservation, has been suggested as an alternative to primary radical radiation therapy, as it would offer an equal measure of tumor control and yet not be as deleterious to the "quality of life."

Such a concern may indeed have merit today in view of modern philosophies of society and newer treatment techniques. In earlier days, the primary interest of the therapist was in the maintenance of life itself, and modifications directed by secondary considerations were unimportant. However, the gradual improvement in treatment techniques (both radiologic and surgical) makes the problem worthy of reconsideration.

Of course, the "quality of life" is difficult to record and measure. The number of divorces may not be "radiation related," but "husband induced." The complaint of dyspareunia may not be due to local vaginal changes, but may involve an emotional etiology. Even osteoporosis can occur in the absence of early castration. The only significant measure we have available to us for analysis is the historical documentation of pertinent patients in follow-up who have been treated in the past. For this reason we have made a retrospective study of the records of such patients, in order to assess the validity of the theoretic assumptions regarding the philosophy of management.

From the Southern California Cancer Center.

Presented by invitation at the Forty-second Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Pebble Beach, California, October 6-11, 1975.

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Materials and methods

From the Tumor Registry of the Los Angeles Tumor Institute and the Southern California Cancer Center, a group of 94 patients, aged 39 years or younger, were collected over the years 1942 to 1972, inclusive (Table I). These patients all had invasive carcinoma of the uterine cervix confined to local organ on clinical evaluation (Stage I_B F.I.G.O.). Cases with microinvasion (Stage I_A F.I.G.O.) were excluded.

To evaluate the incidence of this clinical situation, it is necessary to compare its incidence to that of all cervical cancers, to all Stage I carcinomas, and to carcinoma in situ within our experience. It has been suggested that invasive carcinoma is decreasing because the diagnosis of preinvasive carcinoma has increased. Primarily, this has been attributed to the general acceptance of the Papanicolaou smear in early detection.[1, 2] If this be true, one would expect that invasive carcinoma, too, would be diagnosed in its

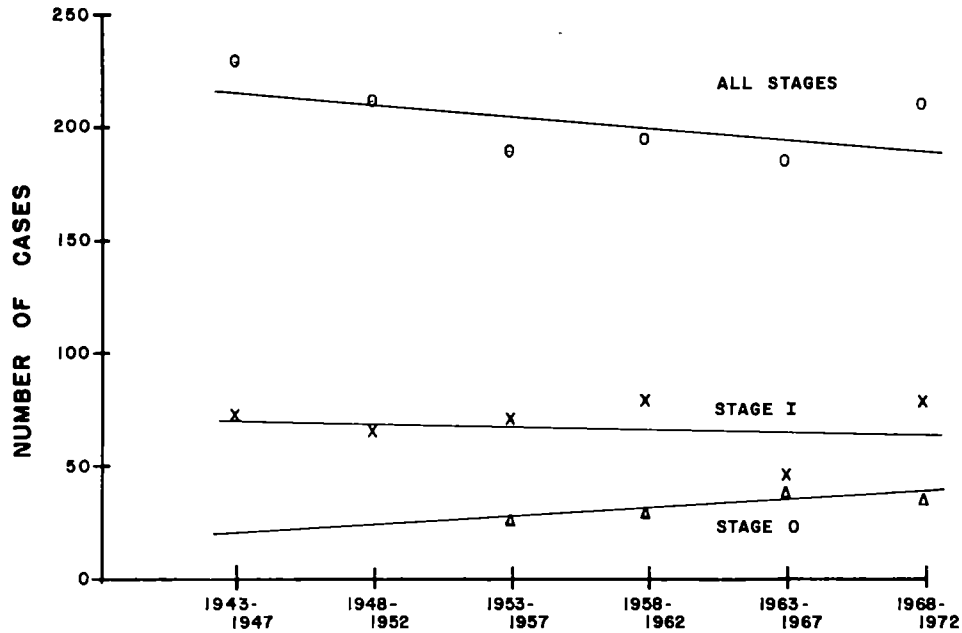


Fig. 1. Carcinoma cervix uteri: Incidence of Stage I cases in relation to all stages and carcinoma in situ.

earliest stages and that it would appear in younger individuals.

Results

The records available to us of patients diagnosed over the 30 year study period in question show that great yearly variation in numbers of patients with all stages, as well as of patients with Stage I disease, occurs. However, when charted in increments of 5 years, the proportionate number of Stage I patients appears only slightly higher in more recent years (Fig. 1). Similarly, once the diagnosis of carcinoma in situ was accepted as a distinct entity, it too appears only slightly higher in the recent time intervals. This, of course, may be due to the fact that carcinoma in situ is usually treated where diagnosed and not referred to an oncology center unless it recurs.

The incidence of Stage I carcinoma in women 39 years of age or younger, as compared to all Stage I carcinomas, does show a gradual increase proportionately in relation to time (Fig. 2). It may well be that the clinical situation is becoming a more important one and deserves consideration.

Another feature that may be of significance lies in the supposition that tumors in young people may be biologically more virulent than in older individuals. When the actuarial survival curve for these 94 patients is compared to that for all the patients with Stage I carcinoma (Fig. 3), it is essentially the same at 5 years and somewhat better at the end of 10 and 20 years.

Table I. Carcinoma cervix uteri, Stage I, Incidence in patients 39 years of age or younger, and method of management*

Patients diagnosed	94
Not treated	4
Primary radiation	76
Primary surgery	14

*Age, ≤39 years; range, 16 to 39 years; mean, 35 years.

Even though treatment methods have been improved and perhaps become more vigorous in recent years, the basic responses do not seem to differ greatly in the patients of the younger age group. It would seem, then, that a review of the clinical courses of this small group of young women may be instructive.

Of the 94 patients in question, 90 received and completed primary radical treatment with intent of cure. Four patients did not complete the prescribed treatment or sought it elsewhere (Table I).

Radical surgical therapy. In the treated group, there were 14 patients who were subjected to radical surgery, and of these, three showed eventual treatment failure (Table II). Since the primary mode of management was radiation therapy during the major portion of this study, the patients receiving primary surgery were a highly selected group and most of the operations were performed within the latter years of the study. These included the younger women with minimal lesions, patients considered good risks for surgery, and some having primary adenocarcinomas.

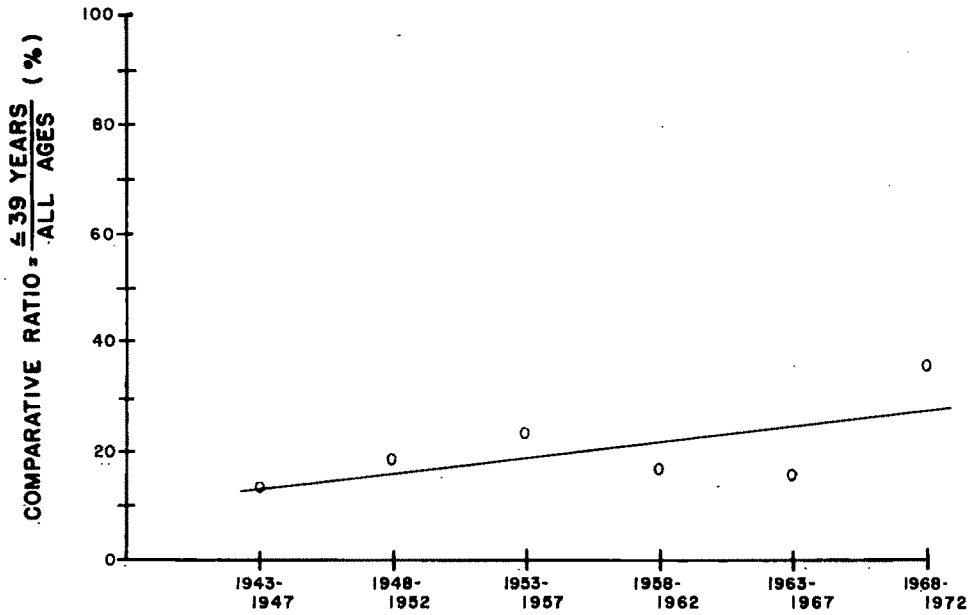


Fig. 2. Carcinoma cervix uteri, Stage I: Comparative ratio of incidence in patients 39 years of age or younger and patients of all ages.

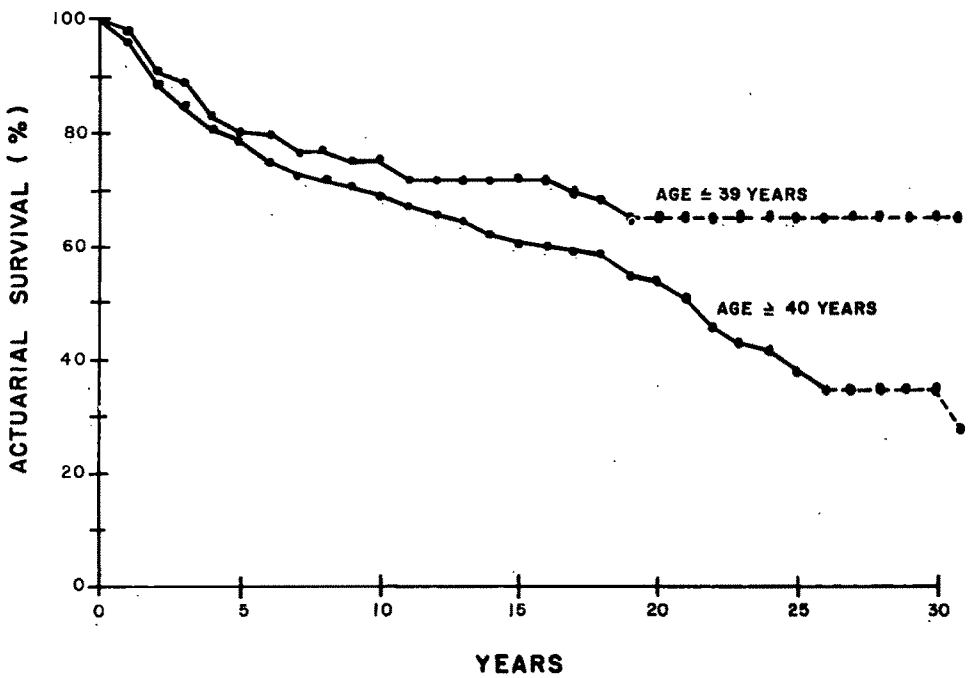


Fig. 3. Carcinoma cervix uteri, Stage I: Comparative actuarial survival rates in treated patients 39 years of age or younger and patients 40 years of age or older.

There were four patients with clear-cell adenocarcinoma of the cervix in this group, one of whom showed local recurrence of the disease in the anterior vaginal wall after 4 years, despite a pathologic report on the operative specimen showing negative lymph nodes and cleared surgical margins.

The other two surgical failures were local recurrences of primary epidermoid carcinomas, with failure at 1 and 2 years, again despite favorable pathologic reports on the excised specimens. Even with this small series, it cannot be said that primary radical surgery will be universally successful.

Table II. Carcinoma cervix uteri, Stage I, in patients 39 years of age or younger treated by primary surgery—incidence of adenocarcinoma and epidermoid carcinoma in relation to success or failure*

	Success	*Failure*
Clear-cell adenocarcinoma	3	1
Epidermoid carcinoma	8	2
Totals	11	3
	(79%)	(21%)

*Primary radical hysterectomy with node dissection: 14 patients; age, ≤39 years.

Table III. Carcinoma cervix uteri, Stage I, in patients 39 years of age or younger treated by primary radiation therapy—incidence of adenocarcinoma and epidermoid carcinoma in relation to success or failure*

	Success	*Failure*
Adenocarcinoma	1	3
Epidermoid carcinoma	48	24
Totals	49	27
	(65%)	(35%)
Complications: Factitial proctitis		3

*Primary external and intracavitary radiation; age, ≤39 years.

Table IV. Carcinoma cervix uteri, Stage I, in patients 39 years of age or younger considered as failures to primary radiation therapy—type of recurrence and time after treatment are indicated

Primary radiation failures			27
Distant spread		5	
Under 2 years	3		
2-4 years	2		
Local and distant spread		10	
Under 2 years	4		
2-4 years	4		
8-18 years	2		
Local disease		12	
Epidermoid carcinoma	9		
Under 2 years	3		
2-4 years	2		
10-27 years	4		
New histology	3		
10-15 years	3		

There was only one patient with a major complication attributed to the procedure, and that was bladder atony. There were no primary surgical deaths, fistulas, or obstructive phenomena.

Radiation therapy. There were 76 patients managed by primary radiation therapy (Table III). Of these, 49 individuals (or only 64.4 per cent) were considered completely controlled throughout their follow-up time at risk. Of these 49, 47 patients are presently alive without disease and without recurrence, and two patients have died without disease. The remaining 27 patients were thought to be primary treatment failures, and can be considered in three groups (Table IV).

Recurrent disease. There were five individuals who showed at least temporary local control, but succumbed rather promptly to distant spread of disease within 2 to 4 years in follow-up. Their deaths were associated with lung, liver, and periaortic nodal metastases. With such histories, one would speculate that these individuals had imperceptible spread of the disease at the time of initiation of local treatment.

There were 10 patients who failed with evidence of local persistence or recurrence of tumor in addition to distant spread. This result, in general, occurred promptly, with four of them showing failure within 1 year, and four others between 2 and 4 years. However, two of them were alive and well for 8 to 18 years, respectively.

This late generalized dormancy is difficult to explain, but leads to speculation that there may have been a breakdown in the immunologic defenses of the patient, or that this represents a new tumor, "radiation induced."

The histories of the 12 patients who were considered to be failures because of local disease offer further interesting observations. Three of these women showed evidence of cervical tumors of a different histologic character from 10 to 15 years in follow-up. One was an adenocarcinoma and one a carcinosarcoma; another a heterologous mesodermal sarcoma. Again, one would speculate that such new tumors were "radiation induced."

Five of the local failures occurred within 3 years of the primary treatment, and of these, three were within one year. However, the remaining four locally recurrent epidermoid cancers recurred after 10 to 27 years in follow-up. Although the early local failures can be attributed to poor or inadequate treatment, the late local failures, again, raise the possibility that they could be associated with the primary treatment itself. It is interesting to note that one patient with a late (27 years) and confirmed positive biopsy of the cervix, refused secondary treatment and has survived, seemingly without further evidence of disease, for another 5 years. The validity of the biopsy report could be questioned, or it may be speculated that the local procedure removed all of the viable disease. Another patient had local recurrence after 17 years, received no secondary treatment, and died 1 year later with distant metastases.

Secondary therapy for recurrent disease. Ten of the patients with local recurrence of residual disease were subjected to secondary therapy. This was successful in six instances, and not successful in four. Surgery was used in five of the successful circumstances, which included three radical hysterectomies and two pelvic exenterations. These included patients who had recurrent disease from 2 to 15 years after primary treatment. Only one was treated by further local radium successfully, and this was a recurrence at 6 months, probably representing residual tumor growth.

Three of the secondary treatment failures were associated with radical hysterectomy, and one with secondary radiation therapy. In the latter instance, a secondary radium application was used for presumed local residual disease 6 months after completion of primary therapy. Although secondary treatment in the face of local persistence or recurrence was not universally successful, the salvage was higher than might be expected, especially in patients with late evidence of disease.

Comment

This study does not purport to be a prospective, randomized, double-blind, clinically controlled experiment. It merely reports a retrospective experience that may have some usefulness. The question raised was that of the possible place of a radical hysterectomy, rather than radical radiation therapy, as the primary treatment for young women with cervical carcinoma. Only one facet of the problem is explored, and that is the fate of these individuals primarily treated, from a long-term point of view.

This study indicates that, although standard actuarial survival rates are similar, the patients harboring the treated local organ are subject to late recurrences or new tumors. Of 42 patients, 10 or more years at risk, some eight (19 per cent) showed such findings. Although a few of these evidenced tumors of different histologic types, most of them were epidermoid cancers, as in the original biopsy specimen. The question is raised as to whether or not these may be "radiation induced," rather than recurrences of the original primary. Furthermore, the study shows that a good proportion of the late local recurrences may be controlled by secondary surgical procedures.

An approach to this problem might be a planned "prophylactic simple hysterectomy" after total radiation. This concept was first proposed by Schyott-Rivers[6] and has been advocated by Durrance, Fletcher, and Rutledge[7] and others[8] in special clinical situations. Such situations include the "barrel-shaped" central cervical tumor, primary adenocarcinoma of the cervix, and primary adenocarcinoma of the corpus with cervical infiltration. The present study indicates that localized carcinoma of the cervix in young women may present another "special clinical situation" which demands individualization of treatment.[9]

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Discussion

JOHN J. MOLITOR, M.D., Fullerton, California. Dr. Futoran has reviewed a 30 year experience at his institution with Stage Ib carcinoma of the cervix in women under the age of 39. The majority of the patients were treated with radiation and, although the numbers are small, his 5 year survival rates were almost identical for radiation and surgery, being 76 and 79 per cent, respectively. Current reports in the literature show 5 year survivals of 88 to 93 per cent for radiation or surgery in Stage Ib carcinoma of the cervix. These recent reports undoubtedly reflect improved radium technique and the use of megavoltage external therapy. Durrance, Fletcher, and Rutledge[1] reported a 50 per cent reduction of central recurrences in Stages I and II carcinomas of the cervix treated with megavoltage as compared to orthovoltage therapy. It would be of interest to know if Dr. Futoran's results have

significantly improved in the later years of his study as compared to the earlier ones. This, I think, is important because Stage I lesions are increasing. For example, in 1959, in New York State, excluding New York City, there were 749 cases of invasive cancer of the cervix. Of these, 424 (57 per cent) were Stage I. While we still see late lesions in the large county hospitals, early lesions are almost the rule in the private hospital.

The authors have considered their late recurrences in detail, noting eight of them occurring 10 to 27 years following radiation. Some of these were of different histologic type from the primary. The facts of late recurrence and different histologic type make them feel that these recurrences may be radiation induced and so they advocate postradiation simple hysterectomy. I am not convinced of the merit of this suggestion for the following reasons. (1) They have shown that secondary treatment of the local recurrences cured 60 per cent of them. So, based on their series of 76 patients managed by primary radiation therapy, this means that 76 postradiation hysterectomies would have been of potential benefit to only three women. (2) If these late recurrences were truly radiation induced, simple hysterectomy removes only a small portion of the total tissue at risk.

Roentgen discovered the rays that "make darkness visible" in 1895 and within 6 years there was published the first case of radiation-induced cancer in man, an epithelioma of the hand with metastases in the regional lymph nodes. Since that time the subject of radiation-induced cancer has been of enduring interest. In 1957 Sir Stanford Cade[2] stated, "The study of radiation-induced cancer in man shows that during the past 50 years there have been two peaks of increased incidence of cancer attributable to radiation. The first peak was immediate, affected the workers, produced cancer in locally damaged tissues, and showed a latent period of 6 to 20 years. The second peak affected patients, nearly exclusively those with benign conditions; the latent period was much longer, 10 to 50 years; the type of cancer included sarcoma and carcinoma; all tissues within the range of radiation were affected." In 1956 Palmer and Spratt[3] reported 61 cancers in the structures within the range of previous radiation in 721 patients who had had radiation therapy for benign uterine conditions and who were followed for an average period of 16.08 years. The sites included uterine corpus, cervix, ovary, rectum, bladder, vagina, and vulva. They also studied 471 patients who had cancer of the cervix treated with radiation during the same time period and followed for an average of 16 years. In these, 13 pelvic cancers developed following irradiation. The incidence of this occurrence was 8.43 per cent in patients irradiated for benign disease as compared to 2.75 per cent in those irradiated for cancer. They postulated a possible stimulating or growth-inducing influence of a relatively low dose of radiation. They believed that the relatively low irradiation dosage given to the group with benign lesions caused some growth-stimulating influence that the higher cancerocidal dosage does not cause.

Durrance and associates[1] in a study of 1,341 patients with Stages, I and II lesions treated radiologically found 13 patients with no evidence of recurrence who many years later developed new lesions of the lower one third of the vagina. They also had nine central recurrences developing 5 or more years after primary therapy. Six of the nine had the appearance of new primary lesions. They suggest that new primary lesions can evolve on the irradiated cervix or in the upper vagina as well as the lower vagina following radiation.

The apparent role that radiation may play in the induction of these neoplasms is fascinating but at present poorly understood. Cole and Nowell[4] have described a possible sequence of events in radiation carcinogenesis based on their work in mice. They attempted to incorporate in their concept many complex interactions appearing at subcellular, cellular, and whole-organ levels. The first step described in the sequence of events necessitates production of a specific genetic alteration (Somatic mutation) in one of a small number of irradiated cells. This effect may be produced by the direct action of radiation therapy on the genetic apparatus or indirectly by primary damage to extragenetic sites or activation of a latent virus. When the specifically mutated cell has entered into mitosis, the neoplasm may be said to have begun its development. Most mammalian neoplasms examined to date, in their late stages, consist of one or a few clones of cells which are markedly altered genetically. Chromosome studies have indicated that nearly all malignant neoplasms consist of a single, or a very few, stemlines of cells with a particular chromosome aberration. Once the specific mutation or mutations have been produced in the irradiated cell, it is also necessary that the cell survive with its proliferative capacity intact if it is ultimately to produce a tumor. A highly mutogenic agent such as ionizing radiation could kill or sterilize a cell so that it is effectively removed from the population at risk. This may explain the higher frequency of neoplasms in patients irradiated for benign uterine disease compared to those treated for carcinoma. If, in fact, radiation carcinogenesis depends on the survival of specifically mutated cells, then the number of tumors which develop will depend on the relative shapes of two dose-response curves, the curve for production of carcinogenic mutations and the curve for cell killing or sterilization. Curves for the former have not been drawn as yet because there is no accurate means of measuring carcinogenic mutations. This will require extension of present chromosome studies to subchromosomal and perhaps to the molecular level. If such a measure were developed it might be of

considerable value in predicting for human subjects the carcinogenic potential of all doses of radiation.

Dr. Futoran's study emphasizes the importance of long-term, namely lifetime, follow-up of patients with treated carcinoma of the cervix. In concluding I would like to ask him two questions. (1) What is your current treatment of young otherwise healthy women with Stage I carcinoma of the cervix? (2) Does the possibility of radiation-induced carcinogenesis in these patients with great potential longevity influence your choice of therapy?

Finally, at the present time, if I were an informed young woman with early carcinoma of the cervix, I would select primary surgical therapy, thereby preserving my ovaries and maintaining a moist, supple, functional vagina.

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DR. ERLE HENRIKSEN, Los Angeles, California. Dr. Futoran associates himself with the so-called younger gynecologic group and with this I agree. However, may I suggest that it is later than many realize.

I would like to digress from the presented material and interject some background on the development of our present concept of early cervical carcinoma.

Our present methodology of early diagnosis and thus hopefully curable cervical cancer is of fairly recent origin. In 1929, Dr. J. C. Bloodgood gave a course in surgical pathology in which he held that any clinician could make the diagnosis of cervical cancer by digital examination alone. He emphasized the dangers of biopsy. On the same floor, but at the end of the hall, a course in gynecologic pathology was given by Dr. Emil Novak. The importance of palpation, visualization, and tissue study were stressed. Thus, at final examination time it was important that we knew from which end of the hall came the questions on cervical cancer.

In 1935, I published an article titled "Precancerous and carcinoid lesions of the cervix uteri with comments on the Schiller test," introducing the term "Bowen's-like disease" into the gynecologic literature. I have often apologized for this unfortunate act, as the term "Bowen's disease" continues to be misused. The original Bowen's disease was limited to a specific skin lesion occurring on the palms and soles of arsenical workers.

In 1936, at the Del Monte Hotel in Monterey, one of my subjects before the California Pathological group dealt with "intra-epithelial epithelioma," now accepted as carcinoma in situ. The general pathologists had a field day disputing my contention that the diagnosis of this lesion as a potential carcinoma was permissable. They in turn argued that if invasion was not present it could not be cancerous. I held that before one could grow an oak tree the planted acorn passed through growth changes preceding the appearance of roots. The controversy, in some ways, was enjoyable and stimulating and lasted for several years.

My interest in the natural history of cervical cancer covers many years. The clinical stage of the disease is unpredictable despite the many recent diagnostic adjuvants. It has long been my impression, based on the examination of necropsy material, that between 20 and 25 per cent of the clinical Stage I cases are actually Stage II or more. Certainly, if a Stage I case cannot be cured with a total hysterectomy the clinical estimate of the disease is in error. I also hold that the radiotherapist is short changed when his statistics are compared with those of the surgeon. He should, in all fairness, be given a 20 to 25 per cent bonus. In closing may I add one of my favorite cliches: Dear Lord, may my words always be gracious and kind for tomorrow I may have to eat them.

DR. J. GEORGE MOORE, Los Angeles, California. I rise to applaud Dr. Futoran's paper. I think it has a great deal to suggest. Although it might not prove a great deal statistically, there is a great deal of qualitative nature that we can be guided by.

Those who have watched this field over a number of decades realize that there is a new breed of gynecologic oncologists abroad and they are decreasing the morbidity of radical operations that Dr. Futoran referred to. There is no doubt that over the course of the last 10 years the complications are fewer and more manageable.

I think also that the radiologists have improved their techniques but they have not particularly decreased their morbidity. They are enthusiasts just the same as we surgeons are, and in their efforts to eliminate failures they have increased the amount of irradiation, and have therewith increased morbidity. That is not presently true in the surgical approach to cervical cancer.

Another point I want to discuss, that Dr. Futoran brought out so well in discussing Dr. Quigley's paper: There are cold spots in the irradiation field following the irradiation treatment of cervical cancer. The upper reaches of the corpus is one cold spot, and I know Dr. Lagasse and his group in our department have felt it very important to appraise the histologic extent of the disease, especially into the corpus, and where the curettage shows that the disease does extend into the corpus, postirradiation hysterectomy is almost mandatory. As a matter of fact, the morbidity of this addition is low, and it helps appraise the extent of the disease for the gynecologist and the radiologist later on. This addition is helpful in pointing the way. So I would say that there probably is a great deal of merit in

considering the simple total hysterectomy following irradiation. There is the complaint that the parametrium is really at risk, and that this is what you are not taking care of with the postirradiation hysterectomy. But unless a computer is employed to assure homogeneity of the field of irradiation, usually a hot spot develops just lateral to point A in the parametria, and this area is well irradiated as opposed to the corpus. Consequently, the parametria are not necessarily at high risk for recurrence.

So I would agree with Dr. Futoran in his thesis that surgery is the right approach for young women, and also with his appraisal of Dr. Quigley's thesis that there is a great deal to say for considering a postirradiation hysterectomy.

DR. IVAN LANGLEY, Portland, Oregon. I would like to congratulate Dr. Futoram also on a very excellent presentation and Dr. Moore on his discussion, because I think he has brought out a point that many of us clinically have accepted of radiation-induced cancers, but have overlooked the point of adequately treated patients with questionable radiation-induced tumors.

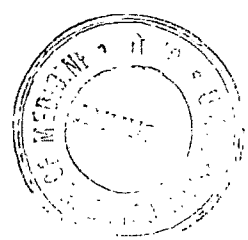
I think, if you really study, as Dr. Molitor has, those statistical situations where radiation is related to tumor development, that the cause is sublethal radiation therapy or exposure.

One thing I would like to ask Dr. Futoran is, in his long-term follow-up, on which he must be congratulated, about the other tumors that these patients are all eligible to develop, bringing in their immunologic possibility and their real defense, not only to carcinoma of the cervix but other malignancies that can be, or will be, developed. Much interest is now being focused in this direction, and really has spurred us to diligent about long-term follow-up. I cannot help but be impressed; clinically, cannot give you statistics now, but I assure you if you have long-term follow-up you will discover that these are high-risk people, not only for carcinoma of the cervix, but for other malignant disease as well.

DR. FUTORAN (Closing). To answer some of Dr. Molitor's questions: Comparing our recent radiation treatment with past treatment modalities would be a little bit difficult. We obtained cobalt in the early 1950's, the Van de Graaff unit in the late 1950's, and in recent years have been using the Betatron on our patients, which is 18 M.E.V. Most of the patients, during this time period, received radiation therapy with either the 1.17 to 1.33 M.E.V. cobalt or 2 M.E.V. Van de Graaff, rather than with higher energy machines.

Our current treatment, and my current treatment may differ from that of my associate, is to use radical surgery when indicated in these patients. There is always the possibility of change in this therapy, but preserving the ovary and the vaginal function is the goal. Radiation-induced tumors are frightening, as Dr. Langley indicated. We looked for, and expected to find, radiation-induced carcinomas of the bladder or rectum in this group, because we have seen such tumors in other patients who have been treated for carcinoma of the cervix. This group of premenopausal women did not present with any of these tumors, except for the sarcomas which were discussed.

Dr. Moore brought up the possibility of staging operations and also discussed Dr. Quigley's article. Staging operations are not being done, at the present time, unless the plan is for a radical hysterectomy. Subjecting the patient to lymph node dissection or to evaluation of the pelvis where hot spots might be produced by radiation therapy seems deleterious. We can radiate them first, explore them, and see if there is tumor along the periaortics or pelvic lymph nodes. Simple hysterectomy and evaluation of the pelvis for other disease would follow, and further radiation therapy would be given, as necessary. This may be the therapy of choice for the future.



Changing trends in cesarean section

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There have been considerable changes in obstetric practice in the past 5 years, with corresponding changes in the application of cesarean section to obstetric complications. In this paper, 4,003 cesarean sections done in a public hospital during four time periods dating back to 1948 are compared, and the changing applications of section are discussed. Breech presentation, fetal distress, and dystocia have contributed substantially to the increasing use of abdominal delivery.

THE CESAREAN section rate in public hospitals traditionally has been substantially lower than the rates reported from many private institutions. But the impetus provided by recent technologic advances and the recognition of a need to enlarge the fetal indications for section have combined to reduce that difference. As an example, the section rate at the Los Angeles County–University of Southern California Medical Center has almost doubled in the past few years to a level comparable to that of the private sector. This paper deals with the changes in obstetric practice that have led to that result and the improvements in perinatal morbidity and mortality rates that have been achieved.

Material

This study is an analysis of cesarean section during four separate periods of time between the years 1948 and 1974[1, 2] and involving 4,003 sections done during the course of 78,017 deliveries (Table I). A majority of the patient population could be classified as at "high risk" on the basis of economic status and limited prenatal care. That the element of risk has diminished over the study period is suggested by several observations. Most importantly, there has been a steady decline in premature births: from 153 per 1,000 in 1959 to 75 per 1,000 in 1974—a reduction of over 50 per cent. There has also been a reduction in the number of infants suffering from intrauterine growth retardation: in 1965-6, 11 per cent of infants born of a patient with a presumably uncomplicated repeat cesarean section had a birth weight in the lowest tenth percentile as compared to a figure of 2.6 per cent for a similar group born in 1974. A third observation is a reduction of approximately 45 per cent in new mothers 17 years of age or younger. Quite possibly this phenomenon is the result of the liberalization of abortion in California in 1969.

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Incidence

The cesarean section rate rose gradually between 1948 and 1969 from a level of 3 per cent to almost 6 per cent. Since then, it has risen more rapidly to a high of 9.4 per cent in 1970, followed by a slight decline in the last several years. During the period of rapid rise there has been a proportionately greater increase in the primary section rate. For example, the primary rate increased from 2.7 per cent in 1965-6 to 6 per cent in 1974.

Primary section

In Table II, the indications for section during four time periods are expressed in terms of the number of sections per 10,000 births. The figures suggest that the difference between the primary section rate in the first two time periods is largely due to an increased reluctance to perform difficult vaginal operative deliveries, including mid-forceps and internal podalic version with breech extraction. Since 1970 this trend has continued to the point that the only operative vaginal delivery now commonly employed is vacuum extraction. But the bulk of the increase in the primary section rate in the past five years is due to the utilization of abdominal delivery for most breech presentations and for fetal distress as diagnosed by fetal monitoring and scalp vein sampling.

Breech presentation. Approximately one third of primary sections in 1974 were done for the indication of breech presentation. Or, to put it another way, 66.5

Table I. Cesarean section—Los Angeles County–USC Medical Center

Year(s)	*Primary*	*Repeat*	*Total*
1948-53	686	689	1,375
1965-66	330	314	644
1970	615	314	929
1974	705	350	1,050
Totals	2,336	1,667	4,003

per cent of breech infants were born by section (Table III). The exponential increase in abdominal births of breech infants in our hospital (2 per cent in 1949, 4 per cent in 1965, 22 per cent in 1970) mirrors a national trend. The prevailing philosophy is an abdominal delivery for all breech presentations associated with one or more complicating obstetric factors. As a result, abdominal delivery has been extended to both premature breech pregnancy and multiple pregnancy with a first fetus presenting as a breech. In the management of teenage pregnancy, a high incidence of breech presentation is an important factor. In 1965 there were no sections for breech among teenagers; in 1974 there were 20.

Cephalopelvic disproportion, failure to progress, failed vaginal delivery, and other dystocias. In the past few years, the diagnosis of "failure to progress" has been employed with increasing frequency to identify a heterogenous group of patients whose progress in labor is unsatisfactory due to a variety of factors, including a small or poorly shaped pelvis, a large infant, inadequate uterine contractions, and deflexion of the fetal head. Perhaps this new obstetric diagnosis was inspired by the inclusion of the Friedman curve in our labor records. But it may also be an admission of our inability to make clear-cut distinctions among the several diagnoses utilized when progress in labor is unsatisfactory, including cephalopelvic disproportion, failed vaginal delivery, contracted pelvis, and secondary uterine inertia. Another reason why the diagnosis of "cephalopevlic disproportion" is disappearing and the diagnosis of "contracted pelvis" has virtually disappeared may be the fact that x-ray pelvimetry is now seldom employed, and the decision for section is usually based on observation of the progress of labor. As matters stood in 1974, the difference between "failure to progress" and "cephalopelvic disproportion" seemed to be a matter of degree. With smaller infants (average 3,250 grams) the diagnosis is most likely to be "failure to progress" and with larger infants (average 3,550 grams) the diagnosis is more likely to be "cephalopelvic disproportion."

Another development in the management of dystocia has been the substitution of vacuum extraction for mid-forceps. While this has yielded good results, it has also been true that many infants appear to be compromised if the vacuum fails and section becomes necessary. For these infants born by section after a failed vacuum extraction in 1974, the incidence of low Apgar scores was 62 per cent at 1 minute and 33 per cent at 5 minutes.

Table II. Cesarean section per 10,000 births

Indication	*1948-53*	*1965-6*	*1970*	*1974*
Repeat section	158	251	321	305
Breech	6	6	92	189
Failure to progress	—	—	193	119
Cephalopelvic disproportion*	63	108	57	38
Failed forceps/ vacuum	1	3	27	25
Fetal distress	2	8	69	87
Placenta previa	29	31	38	37
Abruptio placentae	9	19	15	15
Malpresentation	10	37	45	37
Prolapsed cord	6	19	24	25
Uterine dysfunction	23	36	53	24
Miscellaneous	4	6	15	10
Over-all rate	311	524	949	911

*Includes: contracted pelvis, secondary uterine inertia, and shoulder dystocia.

Table III. Cesarean section, 1974—breech presentation

	Per cent
Term pregnancy	65
Premature pregnancy	64
Multiple pregnancy	83
Primagravida	81
Multigravida	53
Over-all	66.5

Fetal distress. Prior to 1970, a diagnosis of fetal distress was usually made on the basis of pronounced bradycardia which, in the light of more recent knowledge, is often associated with a variable deceleration pattern of fetal heart rate. Eighty per cent of such infants coming to section were born in good condition, consistent with an episode of temporary cord compression to account for the auscultatory findings.

Since 1970, an increasing percentage of patients has been monitored in labor (30 per cent in 1974), and an increasing number of sections are being done for fetal distress—most often on the basis of a late deceleration pattern and usually corroborated by blood-gas determinations of fetal scalp samples. The majority of the infants with a preoperative diagnosis of fetal distress give evidence of depression as confirmed by their

Table IV. Fetal distress: Born by section—Apgar scores

Score	*1 min.*		*5 min.*	
1	14		2	
2	8		1	
3	13		2	
4	8	69%	3	31%
5	8		8	
6	4		9	
7	12		14	
8	6	31%	14	69%
9	7		23	
10	0		4	
Average	4.5		7.4	

Table V. Elective operative procedures

Procedure	*1966*	*1974*
Hysterectomy	46	6
Tubal ligation	134	172
Appendectomy	16	2
Hernia repair	10	0
Salpingo-oophorectomy	1	2
Incidence/section	32%	18%

Apgar scores (Table IV). At one minute, 69 per cent of 87 presumeably distressed infants born by section in 1974 had an Apgar score of 6 or less. At 5 minutes, 31 per cent had a score of 6 or less and 14 per cent had a score of 7. By way of contrast, over 99 per cent of term infants born of an uncomplicated cesarean section had a 5 minute Apgar score of 8 or better.

Malpresentation. Vaginal operative deliveries in the face of malpresentation have rarely been attempted in the last 10 years unless the fetus was both small and dying, or dead. Even the larger stillborn infants are born by section, some deliberately and others because the fact of fetal death could not be established with certainty. The operation of internal podalic version with breech extraction is almost exclusively reserved for an occasional second twin.

Uterine dysfunction. As defined here, uterine dysfunction includes those cases where induction of labor was unsuccessful because uterine contractions were ineffectual, plus a few cases of hypertonic labor. Between 1970 and 1974, the number of such cases has diminished, possibly because of fetoplacental function such as serial estradiol determinations and the oxytocin challenge test have encouraged us to avoid attempts at premature induction of labor for a number of cases where induction might fail. As an example, we no longer arbitrarily terminate the pregnancies of diabetic mothers prior to term as long as the above-mentioned tests are normal.

Other indications. For other surgical indications, including placenta previa, abruptio placentae, and prolapsed cord, the section rate was relatively low in the 1948-53 era, a time when forceful vaginal deliveries were more acceptable and the interest of the fetus of lesser concern. By 1965 these philosophies were no longer attractive, and by 1974 they had been abandoned. As an illustration of our changing attitude toward the fetus, there were three sections done in 1974 for a second twin after the first twin had been born vaginally.

Repeat cesarean section

Our invariable policy has been to perform repeat cesarean section unless the patient is admitted in an advanced active labor. Prior to 1970 this had resulted in an abdominal delivery of 95 per cent of these patients and an approximately equal ratio of primary to repeat sections. Since 1970, the ratio of primary to repeat section has changed to 2 : 1, not on the basis of a higher sterilization rate or more frequent vaginal delivery, but because fewer of the previously sectioned patients are becoming pregnant or, if pregnant, are electing an abortion.

Up until the last few years we did relatively few elective repeat sections (13 per cent in 1965-6), preferring to await the onset of spontaneous labor as a guard against an inadvertent elective premature delivery. Although this policy seemed best for a group of women with uncertain menstrual history and little early prenatal care, there is always the possibility of uterine rupture, particularly if the previous operative incision has been made in the upper uterine segment. In this study, there were 15 uterine ruptures following a previous section and resulting in 11 perinatal deaths; but only one clinically significant rupture followed low cervical section. Our incidence of asymptomatic defects in lower segment scars is slightly less than 1 per cent.

With the advent of newer tests of fetal maturation, our elective rate for repeat section has risen to 25 percent. The results have been satisfactory in terms of avoiding prematurity and respiratory distress, but amniotic fluid analysis has its own hazards. In 1974, two fetuses were lost as a result of an accident of amniocentesis and there were two cases of severe amnionitis that may have been the result of amniocentesis.

Elective operative procedures

While the number of sections has increased, elective operative procedures performed at the time of sec-

Table VI. Operative complications, 1965-6

	No.
Urinary infection	136
Endometritis/parametritis	115
Wound infection	38
Peritonitis	3
Respiratory infection	23
Other	11
Thrombosis	15
Pulmonary embolus	1
Operative hemorrhage	21
Hematoma	3
Defibrination	1
Paralytic ileus	7
Evisceration	1
Vesicovaginal fistula	1
Retained sponge	1
Spinal hypotension	6
Incidence	48%

tion have declined (Table V). This development is partly the result of a new conservatism which holds that additional surgery is frequently not justified because of an expected increase in complications. For example, in the case of hysterectomy for sterilization, our past experience has been that over 50 per cent of the patients will require one or more transfusions, that the average estimated blood loss will be nearly 1,000 c.c., and that the complication rate is almost 70 percent. On the other hand, some elective procedures, such as the repair of small umbilical hernia, do not appear to add to operative morbidity.

Elective sterilization

Between 1965 and 1974, the sterilization rate at the time of repeat section has declined slightly (from 5.7 to 5.1 per cent) despite our increasing willingness to sterilize patients at a younger age and lesser parity. In 1974 there were only half a dozen hysterectomies. The Pomeroy operation has continued over the years to be the overwhelming popular choice of tubal sterilization despite its known failure rate. We have also observed failures with the Kroener fimbriectomy, but not with either the Irving or Uchida techniques.

Anesthesia

In the last 10 years, the anesthesia for all sections has been either spinal, epidural, or inhalation. As judged by the 5 minute Apgar score of uncomplicated cases, there is no difference between the spinal and epidural anesthesia in terms of the condition of the newborn infant. In the case of the inhalation anesthesia, the results are also quite satisfactory, but there have been fewer infants with a 5 minute score of 10, and more infants with a score of 8, a finding that is in keeping with our clinical impression that inhalation anesthesia results in a slight depression of the neonate.

In comparing 1965-6 with 1974, the average 5 minute Apgar score of uncomplicated cases in the later period is significantly higher: inhalation 8.3 vs. 9.1, epidural 8.6 vs. 9.3, and spinal 8.3 vs. 9.3. Quite possibly this improvement is due to the better quality of anesthesia that can be provided by anesthesiologists specializing in obstetric anesthesia, not only in the administration of the anesthetic, but also in providing for more attention to the maintenance of fetal integrity during the period of surgical preparation, and better infant resuscitation. The efficacy of current resuscitation is suggested by a reduction in low 5 minute Apgar score (6 or less) from 20 to 3 per cent.

Table VII. Postoperative readmission: 1974

Diagnosis	*No.*
Hemorrhage—curettage	2
Hemorrhage—hysterectomy	3
Hematoma	4
Endoparametritis	5
Wound abscess	2
Ovarian abscess—hysterectomy	1
Dehiscence	1
Evisceration	1
Thrombophlebitis	2
Pulmonary embolus	2
Renal failure	1
Incidence	2%

Table VIII. Perinatal deaths: Indication for section

Indication	*1948-53*	*1965-66*	*1974*
Previous section	1.7	2.6	0.9
Abruptio placentae	68	19	6
Placenta previa	21	24	7
Dystocia*	7	3	0.5
Prolapsed Cord	11	7	7
Malpresentation	19	7	7
Uterine malfunction	19	18	4
Breech	0	0	4
Fetal distress	—	10	7
Miscellaneous	20	14	0
Over-all	8.7	6.6	2.8

*Includes cephalopelvic disproportion, contracted pelvis, shoulder dystocia, and failed vaginal delivery.

Operative complications

In assessing abdominal delivery, the increased morbidity of a major surgical procedure is an important consideration. Although cesarean section is considered to be one of the safest of all major operations, and conceding the fact that morbidity should be greater in the particular population under study, almost half of

Table IX. Lethal congenital defects: Cesarean section

Years	*Indication for section*	*Defect*
1965-6	Dystocia	Meningocele
1974	Previous section	Anencephalus*
	Dystocia	Anencephalus*
	Breech	Conjoined Twin
	Breech	Conjoined Twin
	Breech	Meningocele
	Breech	Absent Diaphragm
	Breech	Anencephalus
	Breech	Meningocele
	Malpresentation	Hydrocephalus*
	Malpresentation	Anencephalus
	Fetal distress	Multiple abn.
	Fetal distress	Cor trilocularis

*Stillborn.

the patients in each time period had one or more operative complications, including a respectable number of severe complications which compromise future childbearing or are potentially lethal. In 1965-6, a dozen patients had dangerous complications requiring prolonged hospitalization (Table VI). In 1974, the situation was unchanged. As is shown in Table VII, 2 per cent of the patients undergoing section were readmitted for the treatment of operative complications, including four women requiring a subsequent hysterectomy. There were eleven maternal deaths among 4,003 sections, of which seven were due to operative complications, including infection (3), anesthetic accident (2), operative trauma (1), and pulmonary embolus (1).

An operation currently being revived for grossly infected cases is extraperitoneal section. Our experience has largely been confined to the Norton procedure. Because of its paravesical approach, this operation risks trauma to the ureter and the deep pelvic blood vessels. Among 130 women treated by a Norton extraperitoneal section during the period of study, one patient died as the result of uncontrollable paravesical hemorrhage and another patient required a nephrectomy because sutures employed to control paravesical hemorrhage had damaged the left ureter.

Perinatal deaths

There has been a continuing decline in perinatal morbidity among infants born by sections: 8.7 per cent in 1948-53, 6.6 per cent in 1965-6, and 2.8 per cent in 1974 (Table VIII). But there has been no increased statistical advantage to abdominal delivery because there have also been identical decreases in the perinatal mortality rates of vaginal delivery. Perhaps this observation should serve to remind us that a great deal of the improvement in obstetric outcome is due to the advances in neonatal care.

Almost all of the increases in the survival of infants born by section in the past 10 years has been among term-sized infants. In comparing 1965-6 with 1974, the mortality rates among premature infants were 17.2 and 15.6 per cent; the mortality rate among term infants fell from 4.2 to 0.8 per cent, with a better survival in all groups with the exception of breech presentation (seldom an indication for section in 1965-6). Term infants have benefitted not only from technologic advances, but also from our capability to hospitalize mothers for extended periods of time during which fetal maturation has been achieved. As an example, some mothers with diabetes have been hospitalized for as long as 6 weeks, at a cost which would be prohibitive without financial assistance or subsidy.

Our failure to reduce the gross perinatal mortality rate of premature infants is possibly due to the increased utilization of section for breech presentation and malpresentation, two categories with a high perinatal mortality rate. Another factor of probable importance—although difficult to measure—is a willingness to perform a section for small infants with a limited potential for survival. Because of the considerable recent improvements in the care of the small neonate, an optimistic attitude seems amply justified. Our over-all survival rates for infants born in 1974 are as follows: 68 per cent for infants weighing 1,001 to 1,500 grams, 91 per cent for infants weighing 1,501 to 2,000 grams, and 92 per cent for infants weighing less than 1,000 grams and born by section. One other factor bearing upon perinatal death is a decline in premature births by section from 19 to 10.7 per cent, exactly paralleling the fall in the over-all rate of premature births.

One of the hazards of liberalizing indications for cesarean section appears to be the possibility of increasing the number of infants born by section having lethal congenital defect. Such defects are likely to be associated with breech presentation, malpresentation, or fetal distress. These possibilities are born out by our experience in 1974, during which 12 infants with lethal congenital defects were born by section as compared with one such infant in 1965-6 (Table IX).

Perinatal morbidity

The 5 minute Apgar score provides a rough indicator for perinatal morbidity. Over the last 10 years the incidence of morbidity has been 25 per cent for a score of 1 to 3, 10 per cent for a score of 4 to 7, and 1.7

per cent for a score of 8 or more. On more detailed analysis, 70 per cent of morbidity is due to respiratory distress and 90 per cent of the affected infants will have been affected by prematurity, intrauterine growth retardation, obstetric shock, or maternal diabetes.

Only a small number of infants show unequivocal evidence of brain damage: three in 1965-6 and two in 1974. Perhaps twice as many infants had neurologic manifestations which seem to clear, but the ultimate outcome is unknown.

Comment

During the last quarter century, the application of cesarean section to the practice of obstetrics has undergone considerable change. In the beginning, there was a gradual increase in the utilization of abdominal delivery which can be ascribed to a number of factors, including an acceptance of the increased safety of major surgery and the declining influence of an older generation of obstetricians trained to solve obstetric difficulties by means of vaginal operative procedures. As time went on, the impetus toward abdominal delivery was strengthened by a realization that improved care of the neonate expanded the fetal indications for section by virtue of the increased prospects for infant survival. More recently, the emphasis has shifted from reducing perinatal deaths to a reduction in perinatal morbidity and the elimination of the long-term consequences of the complications of birth.

To the end of reducing perinatal morbidity, the advances in assessing fetal maturation and fetal well-being, and the increasing utilization of fetal monitoring, have improved our ability to select cesarean section in a more efficient manner, but at the same time increasing the section rate because it is now possible to recognize a much greater percentage of those cases for which a vaginal delivery is unfeasible or undesirable. Probably most fetuses now being identified as having evidence of distress would have survived without the benefit of these advances. The question is: would they have been unnecessarily damaged in the process?

The major consideration in our desire to decrease perinatal morbidity is a reluctance to risk a potential traumatic delivery. As previously mentioned, this desire began with abandonment during the 1950's of the more spectacular vaginal maneuvers such as internal podalic version and has culminated in the virtual elimination of breech birth except for those cases where time does not permit surgery or the prospects for survival of the fetus are nil.

The wisdom of a more liberal utilization of cesarean section is difficult to judge. A comparison of the results in different periods of time is hampered by change in the patient population, in prevalent obstetric risks, in newborn care, in the quality of obstetric anesthesia, in prematurity rates, and in technologic advances. What is most needed, and least available, is an adequate long-term evaluation of the impact of delivery upon the developing child.

At the present time, a cesarean section seems to be indicated for almost any obstetric difficulty as the only means of avoiding the unpredictable bad result of vaginal birth. The only constraining counter argument is the realization that abdominal delivery still carries additional maternal risk, disability, and expense.

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Discussion

Dr. William F. Kroener, Jr., Whittier, California. Dr. Hibbard's paper clearly reflects a change in emphasis from protection of the mother to protection of the mother *and* neonate which has occurred over the past quarter century. This shifting emphasis has been brought about by a number of factors. The improvement in operative technique, obstetric anesthesia, and postoperative care has progressively reduced the maternal mortality rate for cesarean section to the point where it now approaches the over-all maternal mortality rate. The increasing knowledge concerning fetal well-being has made it possible to more closely determine when the risk to the fetus requires termination of the pregnancy by cesarean section.

At Presbyterian Hospital in Whittier, the section rate has increased from 7 per cent in 1960, when the hospital opened, to 13 per cent in 1974. Where 10 per cent of breech presentations were delivered by cesarean section in 1960, 32 per cent were so terminated in 1974. It was interesting to note that the use of the term "failure to progress," which has largely replaced cephalopelvic disproportion as a diagnosis at Los Angeles County–University of Southern California

Medical Center during the past 5 years, is still wholly lacking in our community hospital records.

One of the long-held principles in obstetrics has been that the cesarean section rate was inversely proportional to the quality of the obstetrics practiced. Any obstetrician with a high section rate was evaluated for the quality of his obstetric care and accused of trying to pad his financial remuneration. I well remember the stress and concern of the surgeons and internists at Good Samaritan Hospital in Los Angeles when, in 1956, we were placed on probationary status by the Joint Commission on Accreditation because the hospital section rate was almost 10 per cent. The entire Obstetrical Staff was almost drummed out of the Corps.

When I reviewed the operative complications on Table VI, I seem to be at odds with Dr. Hibbard's figure of a 48 per cent incidence. My calculation came to 383 complications out of 644 sections, or an incidence of 59 per cent. When I removed the urinary tract infections, namely 136, my incidence of complications came to 38 per cent. Since I was unable to get our figures to agree, I simply accepted his premise that the complication rate was a lot higher than I thought, ±10 per cent. Needless to say, cesarean section does carry a higher morbidity and mortality rate for the mother. Whether this can be further reduced as it has in the past is a matter of concern.

The inclusion of breech presentation with malpresentations as an indication for cesarean section rather than vaginal delivery is the single biggest change which has transpired. As we continue to develop this concept in our residency programs, we will continue to see an increasing cesarean section rate. One can hardly realize that the management of breech presentation by vaginal delivery is rapidly becoming a lost art, even as have deliveries by high forceps, internal podalic version, and mid-forceps been gradually discarded in favor of cesarean section.

The long-held concept of vaginal delivery if at all possible is rapidly giving way. The new growing principle seems to be, *vaginal delivery only of selected patients.* Whether this new concept will result in a reduced maternal mortality rate and a continued reduction in perinatal morbidity remains to be seen. I hope our course is charted in the right direction.

DR. ROBERT C. GOODLIN, San Jose, California. I think we all look with real interest on any of the data from USC because they are in many respects the leader of our specialty. We have found that an undiagnosed abnormal fetus hardly ever makes it through labor in our hospital, that it always showed signs of fetal distress, and that the only way we could avoid doing an emergency cesarean section on a fetus with anomalies that were incompatible with life was to make the diagnosis somehow before labor. I have been told this had not been the experience at USC but I wonder how many of those fetuses with anomalies that were incompatible with life did have signs of fetal distress and have emergency cesarean sections?

I would think that if one's primary cesarean section rate was very high that the repeat cesarean section rate would also have to increase, but I did not see that in the data. And I wonder if women who have had previous cesarean section are allowed to deliver vaginally?

And the third question concerns the use of antibiotics. Once we started using routine antibiotics at the time of cesarean section, we found that our complication rate was reduced significantly. What is the policy at USC?

DR. HIBBARD (Closing). Some of the patients had more than one operative complication.

Fetal distress was the indication for section of two infants with lethal congenital abnormalities. Possibly some of the others showed evidence of fetal distress, but I do not have that information.

Our policy is to deliver all previous section patients abdominally unless the patient is admitted in advanced labor. As a result, about 95 per cent of patients are sectioned. This means that patients who have had a section are having fewer subsequent babies for a variety of reasons.

I cannot really say much about prophylactic antibiotic drugs. It is my impression that Dr. Ledger has not found them to be of great value in our patients, but I believe that he is now re-examining their efficacy in a prospective study.

Histopathologic evaluation of uteri curetted by flexible suction cannula

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A prospective study was undertaken to evaluate the use of the flexible plastic cannula for obtaining endometrial specimens for diagnostic purposes. Suction curettage was performed immediately prehysterectomy, the specimens evaluated, and then compared to similar specimens obtained by a metal curette. Another group of patients had suction curettage performed as an office procedure 24 to 72 hours before hysterectomy. The results of our study confirm the adequacy of this method for obtaining endometrial samples.

WHILE CYTOLOGIC screening of exfoliated cervical cells is a successful technique for detecting cervical neoplasia, it is much less accurate when used for endometrial cancer screening.[2, 3, 6] Consequently, removal of endometrial tissue for diagnostic evaluation has become the primary method for detection of early endometrial carcinoma in high-risk females. This usually means a dilatation and curettage of the uterus in a hospital operating room. Therefore, it would seem worthwhile to develop modifications that would permit outpatient screening which are safe, efficient, inexpensive, and relatively painless.

At our institution, the use of the small, flexible, plastic cannula for menstrual aspiration and early pregnancy termination has proved to be a highly successful tool.[1, 4, 5] This study was undertaken to evaluate the use of the same instrument in obtaining endometrial specimens for diagnostic purposes.[7, 8]

Materials and methods

Eighty patients who were scheduled for abdominal or vaginal hysterectomy had a suction curettage performed with the flexible plastic cannula immediately prior to their operative procedure. The curettings and uterus were then evaluated microscopically for histologic quality and depth of sampling. The depth was based on the presence or absence of spongy or superficial tissue, compacta or intermediate layer tissue and basal or deep endometrium in the removed uterus. The uteri were also evaluated for residual endometrial tissue in the following sites: isthmus, anterior and posterior mid portion, and right and left cornual regions.

Twenty-three of the uteri were submitted to a detailed microscopic and gross examination. Fifty-seven additional specimens were studied in detail by gross examination alone. Seven specimens were microscopically and grossly evaluated following curettement with only a standard sharp metal curette.

Table I. Suction curettage: Microscopic and macroscopic histopathology (23 cases)

	Superficial		*Intermediate*		*Basal*	
Endometrium removed	*No.*	*%*	*No.*	*%*	*No.*	*%*
Isthmus	23	100	17	74	6	26
Middle:						
Anterior	22	96	15	65	5	22
Posterior	23	100	14	61	4	17
Cornua:						
Right	20	87	9	39	0	
Left	17	74	8	35	0	

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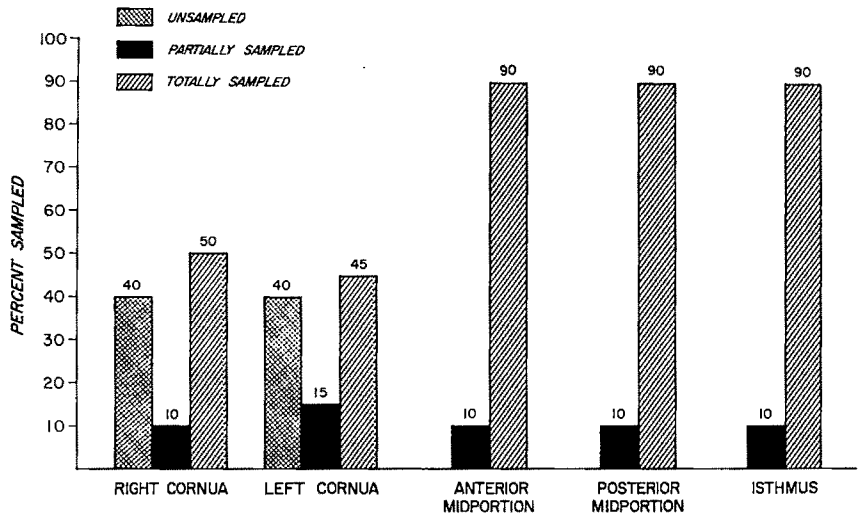


Fig. 1. Macroscopic screening of 57 uteri.

Table II. Metal curettage: Microscopic and macroscopic histopathology (7 cases)

Endometrium removed	*Superficial*		*Intermediate*		*Basal*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Isthmus	7	100	5	71	5	71
Middle:						
Anterior	7	100	5	71	4	57
Posterior	7	100	6	86	5	71
Cornua:						
Right	4	57	2	28	0	
Left	3	43	0		0	

The patients ranged in age between 26 and 75 years with a majority between 35 and 45 years. The primary indications for surgery were sterilization and pelvic relaxation. Other indications included adenomyosis, leiomyomas, and endometriosis.

The cannulas* used for this study were flexible, blunt tipped, with a double aperture at the distal end, and measured 4, 5, and 6 mm. in diameter. Vacuum sources during the procedures were usually a 50 c.c. syringe.† We also used a "bicycle pump" suction apparatus,† an electric pump,* and a "Mity-vac" hand pump.‡ None of the vacuum sources altered the findings presented since all pressures were maintained at about 650 mm. Hg.

Results

Table I reveals the results obtained by careful evaluation of the initial 23 uteri. Grossly and microscopically, the superficial layer of the endometrium was removed completely or nearly completely in the isthmic and mid portions of all but one patient. The superficial endometrium was removed from the right cornua in 20 patients (87 per cent) and from the left cornua in 17 patients (74 per cent).

Table II reveals the results obtained in the seven patients in whom a metal curette was used. Note that the superficial endometrium was removed from the right cornual region in four cases (57 per cent) and from the left in three (43 per cent). The basal endometrium was damaged or removed in the isthmus and mid portions in five (71 per cent) of the patients. Myometrial fragments were found in these five patients.

Fifty-seven additional uteri were screened macroscopically following suction curettage. The results are shown in Fig. 1. The only areas that were inadequately sampled were in the cornua. These areas were interpreted as being incompletely sampled in 40 per cent of these patients.

The use of the suction catheter consistently resulted in larger intact strips of tissue which aided the pathologist in tissue interpretation and diagnosis. Vacuum aspiration did not seem to alter or impair the histologic quality of cellular detail. In one instance an invasive epidermoid carcinoma of the cervix was diagnosed in a 60-year-old postmenopausal woman who presented with abnormal bleeding. The tissue was obtained during diagnostic aspiration utilizing a fractional technique and later confirmed by cone biopsy.

Blood loss in all cases was reported as minimal. There were no uterine perforations reported.

Based on the initial findings with this method of endometrial sampling, an additional 25 patients un-

*Obtained from Berkeley Bio-Engineering, Inc.

†Obtained from Rocket of London, Inc.

‡Obtained from Nalgene, Inc.

derwent office endometrial biopsy with the same procedure except that paracervical block was used for the anesthesia. Although it was impossible to immediately assess the adequacy of sampling, the amount and quality of tissue obtained at hysterectomy 1 to 3 days later was identical to that obtained in the earlier study. In another twenty patients, endometrial biopsy with the 4 mm. cannula was performed without use of any anesthesia. Again, histopathologic evaluation confirmed the adequacy of the specimens.

Comment

Suction curettage with small, flexible cannula removed sufficient endometrium for accurate pathologic diagnosis. The advantages of this technique are less trauma to the basal endometrial layers, a more uniform removal of tissue, and easier access to the cornual regions. The removal of the basal layer and fragmentation of tissue were found to be less extensive with suction when compared to sharp curettage. Because the flexibility of the tip of the cannula decreases the likelihood of penetrating the uterine wall, it should diminish the risk of uterine perforation.

Histologic sampling by the small, flexible cannula may prove advantageous as a screening procedure in high-risk outpatients with or without symptoms. This method of endometrial sampling appeared to be more effective than the traditional sharp metal curette used in the operating room.

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Discussion

DR. HERMAN S. RHU, JR., Tucson, Arizona. This report accurately depicts the efficiency of suction dilatation and curettage (D & C). Its availability and simplicity make it a primary tool for precise evaluation of the endometrium, and especially the early diagnosis of adenocarcinoma of the endometrium. It is an interesting fact that, until many devices were designed for ambulatory suction curettage in conjunction with early abortion, the instrumentation for this type of procedure was for the most part not available. Now there have been many developments in the field of abortion that have been translated into early diagnostic procedures for use in every phase of dysfunctional bleeding. These have resulted in the early diagnosis of endometrial carcinoma or premalignant lesions of the endometrium. This is a "vacuum cleaning device" that operates efficiently and effectively in the uterus. Dr. Hale's studies have clearly shown this. Its accuracy, we know from other studies, is in the neighborhood of 95 to 98 per cent. It certainly is as effective, if not more so, than the expensive procedure of sharp curettage as an in-hospital or an ambulatory-care procedure. It adapts itself well to the office and can be used, therefore, more frequently and more promptly in the management of the dysfunctional bleeding episodes that may be quite grave in nature. Dr. Hale is to be congratulated for his simple and direct approach to this problem. He has added a contribution to the field of early cancer diagnosis. Office endometrial sampling techniques are not new and date back to the days of Howard Kelly at Johns Hopkins. The recent reintroduction of suction D & C techniques and instrumentation have been an outgrowth from the liberalization of abortion. It is now apparent that we have the instrumentation for adequate in-office suction D & C. Comparative studies using various methods of curettage with or without suction indicate that the procedure is as accurate as an in-hospital D & C, probably 95 to 98 per cent. A differential D & C (cervix and uterus) can be carried out in the office. Dr. John Wall of Houston, Texas, described this procedure 15 or 20 years ago, but it was infrequently used until Dr. Fred Hofmeister of Milwaukee, Wisconsin, reported a massive series in the early 1970's (20,677 endometrial biopsies in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, 118: 773-777). About this same time, many other gynecologists began reporting "extended endometrial biopsies," outpatient D & C (Dr. William Mengert), and finally suction D & C procedures with or without anesthesia. Recently, Dr. John Poyas of Newport Beach, California, designed a simple suction apparatus for office use. The Gravlee-Jet Washer has been recently developed and has it own group of enthusiastic followers. It is apparent that liberal use of intrauterine diagnostic techniques has improved the

early diagnosis rate and favorably influenced the management of endometrial cancer and its precursors. The current ratio of cervix to endometrial cancer has approached 1 : 1.

This report neatly analyzes and compares the thoroughness of suction D & C versus in-hospital D & C. Its clear-cut, gross and microscopic slides attest to the completeness of the procedure.

The development of laparoscopy has recently been phenomenal. One cannot resist the opportunity to suggest that its more liberal use in screening the vaguely symptomatic patient with abdominal discomfort and/or pain may result in the early diagnosis of intra-abdominal malignancy and especially carcinoma of the ovary.

DR. ERNEST W. PAGE, Piscataway, New Jersey. There is a certain amount of pain when the cannula is introduced through the internal os. Over the years I have noted that such pain may be markedly reduced by simply soaking a Q-tip in 1 or 2 per cent lidocaine, placing it within the internal os, and leaving it there for a full minute. Many gynecologists are not aware of this, but you may find that it will obviate the need for a paracervical block.

Vaginal reconstruction following extensive treatment for pelvic cancer

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Since 1970, 23 patients at UCLA and The City of Hope who have undergone extensive treatment for pelvic malignancy have had vaginal function successfully restored. A combination of methods, including split-thickness skin graft and the construction of an external vulvar pouch, is often necessary to obtain maximal functional results. The external vulvar pouch was very useful, although not as anatomically appealing as internal methods of reconstruction. In young patients who required an exenteration, a new technique using part of the anterior bladder fundus was developed. Preliminary experience with this method was promising. Among the group of 23 patients, there have been no overt failures. By combining restoration of rectal function with vaginal reconstruction, two major steps have been taken toward total rehabilitation of the patient undergoing extensive treatment for pelvic malignancy. Persistence, ingenuity, and planning by the surgeon are essential to obtain a maximum functional result for each patient.

THE MAJOR considerations in carrying out extensive treatment for pelvic malignancy are control of the disease, minimizing death and morbidity, and rehabilitation of the patient. With improved rates of cure and decreased operative death and morbidity, gynecologic oncologists are now focusing attention on patient rehabilitation. In a previous report by this group, the successful re-establishment of rectal function following pelvic exenteration with a mobilized segment of sigmoid colon was described.[1] Since 1970, 60 patients have undergone pelvic exenteration at UCLA Medical Center and The City of Hope. In 18 of these patients, sigmoid replacement and satisfactory re-establishment of rectal function was possible.

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The absence of adequate vaginal function is a major disability encountered in patients treated for pelvic malignancy by either radiation, or surgery, or both. The present report deals with a group of 23 patients undergoing treatment for a variety of gynecologic malignancies who were in need of vaginal reconstruction. Our search for more effective methods of vaginal reconstruction than currently available was made more urgent by a small group of young women who presented with stilbestrol-related adenocarcinoma of the vagina. In these patients, restoration of adequate vaginal function had obvious importance. An increasing number of older patients being treated for pelvic cancers have also showed marked concern for restoration of sexual function.

Vaginal reconstruction in patients with congenital vaginal atresia was first described by Depuytren[2] in 1817. Since then many techniques have been described and results have generally been successful. Fewer reports are available concerning procedures to restore vaginal function after extensive surgery or radiation therapy for malignant disease, and these results have been far less optimistic. In 1963, West and co-workers[3]

Table I. Patients undergoing vaginal reconstruction following therapy for gynecologic cancer (1970-1974)

Prior surgical procedure		*No. of patients*
Exenteration		14
Total	11	
Anterior	2	
Posterior	1	
Vaginectomy		6
Vaginectomy and vulvectomy		2
Vaginectomy and radical hysterectomy		1
		23*

*Includes 16 patients with prior irradiation therapy.

Table II. Vaginal reconstruction following therapy for gynecologic cancer (1970-1974)

Recurrent cervical	9
Primary cervical	2
Primary vaginal	6
Preinvasive vaginal	6
	23
Prior radiation therapy	16
No prior radiation	7
	23

reported on 12 patients who developed vaginal stenosis following radiation for cervical and vaginal cancers. Good functional results were reported in patients undergoing total vaginectomy and placement of a split thickness skin graft. Pratt and Smith[4] reported on 19 patients who underwent sigmoidoplasty and vaginoplasty with successful restoration of vaginal function. Morley and co-workers[5] more recently reported on 17 patients who underwent vaginal reconstruction following pelvic exenteration and stressed the need for rehabilitation. Fifteen patients in the Michigan series were considered to have had good functional results. Two patients could not be evaluated, one because of early recurrence, and the other due to failure to attempt intercourse. Other single case reports utilizing known approaches to vaginal reconstruction in patients treated for cancer have on occasion appeared in the literature.[6–9]

Materials and methods

The present report concerns vaginal reconstruction in 23 patients who have undergone extensive treatment for malignant disease (Table I). Prior surgery consisted of exenteration in 14 patients, vaginectomy alone in six patients, vaginectomy and vulvectomy in two, and vaginectomy and radical hysterectomy in one patient. Eleven of our patients were treated for cervical cancer and 12 patients had a vaginal malignancy. Six of the patients with vaginal disease had invasive carcinoma and six patients had preinvasive or microinvasive lesions. A history of previous radiation to the vagina was noted in 16 patients and was not considered a contraindication to vaginal reconstruction (Table II).

Four basic surgical techniques with several modifications were employed according to the clinical circumstances encountered (Table III). The most commonly employed procedure was the split-thickness skin graft as described by McIndoe and Banister[10] for congenital vaginal atresia. In the present series, 11 patients were treated with split-thickness skin grafts, and in two patients, skin grafts were used to enhance the depth of an external vulvar pouch. In one case, a skin graft was used in conjunction with a transplanted segment of sigmoid colon.

Vaginal reconstruction in five patients recovering from total pelvic exenteration was performed 3 to 6 weeks postoperatively after the residual cavity had partially granulated. When the granulation bed had adequately formed, a split-thickness skin graft was applied. The major problems encountered with this method concern the contour of the cavity and tendency to progressive fibrosis within the cavity.

The Williams[11] procedure for construction of an external vulvar pouch was employed in seven patients. This method has been elaborated upon recently by Simmons and Millard.[12] The primary indication for use of the external pouch was in patients who had undergone exenteration more than 8 weeks prior to vaginal reconstruction. In the Williams' procedure, an elliptical incision is made near the junction separating the labia minora from the labia majora (Fig. 1, *A*). The skin edges from the medial margin of the incision are approximated in the midline with interrupted polyglycolic acid absorbable sutures, thus creating a new posterior vaginal wall from the labia minora (Fig. 1, *B*, and *C*). The lateral margins of the incision are now sutured in the midline, extending the posterior fourchette and completing the external vaginal pouch (Fig. 1, *D*). Four points in this technique are worthy of note. (1) The depth of the pouch is determined primarily by the length of the lateral incisions and should be made to provide maximum depth. (2) The lateral incisions should not be carried anteriorly past the level of the clitoris or the vagina cannot be easily entered. (3) If the lateral incisions are too medial, the caliber of the vagina will be too small. (4) Initially, the vertical angle of inclination in the long axis of the neovagina will be more anterior than a normal vagina and initial attempts at intromission may be difficult. Later, as tissues soften, the vagina will be inclined in a more

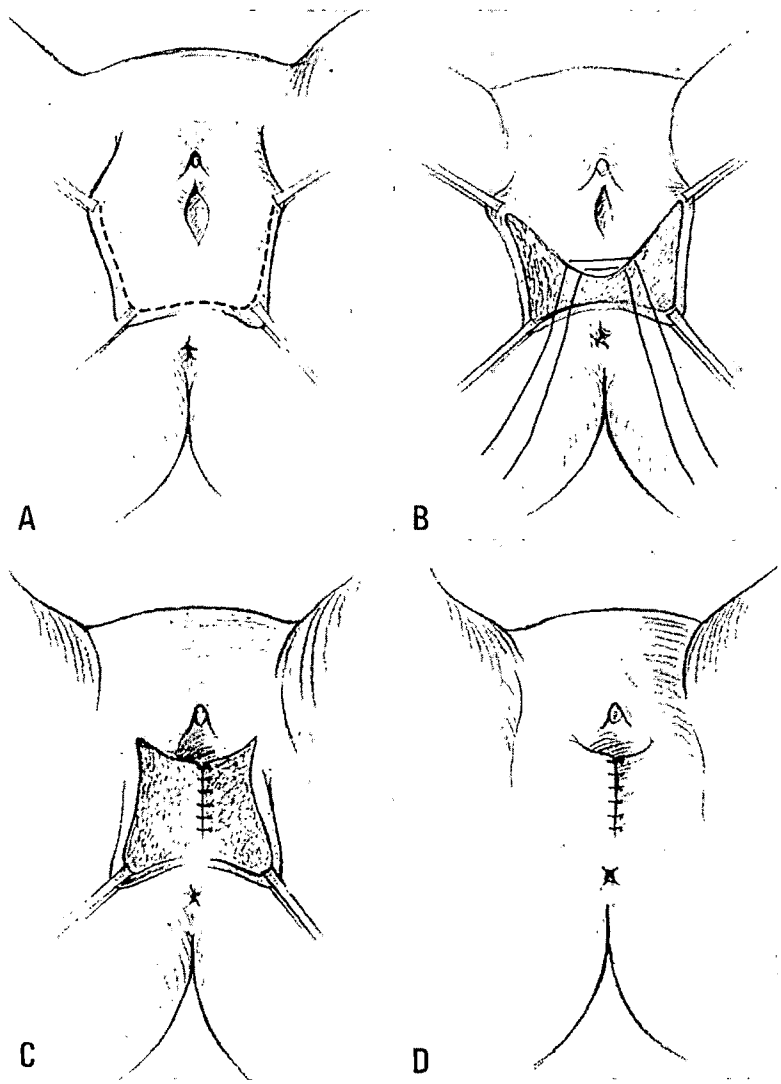


Fig. 1. *A,* The labia majora are retracted laterally with noncrushing clamps. The U-shaped incision is usually made at the mucocutaneous junction between the labia minora and labia majora and continues across the posterior fourchette to the opposite side. The mucosa is undermined posteriorly in the midline to allow for mobilization. *B,* Beginning posteriorly the medial edges of the mucocutaneous incision are approximated with 3-0 interrupted polyglycolic acid sutures. The skin of the labia minora is thus turned inward, becoming the posterior vaginal wall, as depicted in *C. C,* The approximation of the medial edges of the incision is now completed and the posterior vaginal wall constructed. *D,* The lateral edges of the wound are now approximated in the midline with interrupted polyglycolic acid sutures. The labia majora thus form an extension and reinforcement of the perineal body. Note that only two layers are used for closure as the placement of a third subcutaneous layer causes the neovagina to be too constricted and rigid for optimum function.

normal direction. Both the patient and her husband must be made aware of this anatomical variation.

Recently our attention has been directed to the use of the dome of the bladder as a source of tissue for reconstruction of the vagina and pelvic floor at the time of exenteration. Though not previously reported, this method has occasional application in patients with centrally recurrent malignancy without bladder involvement. The procedure was carried out in four patients by preserving the anterior-superior portion of the bladder fundus with the attachments to the superior vesical arteries (Fig. 2). The mucosa of the preserved bladder fundus was dissected from the muscularis and discarded in order to provide an appropriate base for skin grafting. The latter step was deemed necessary because of the known propensity of

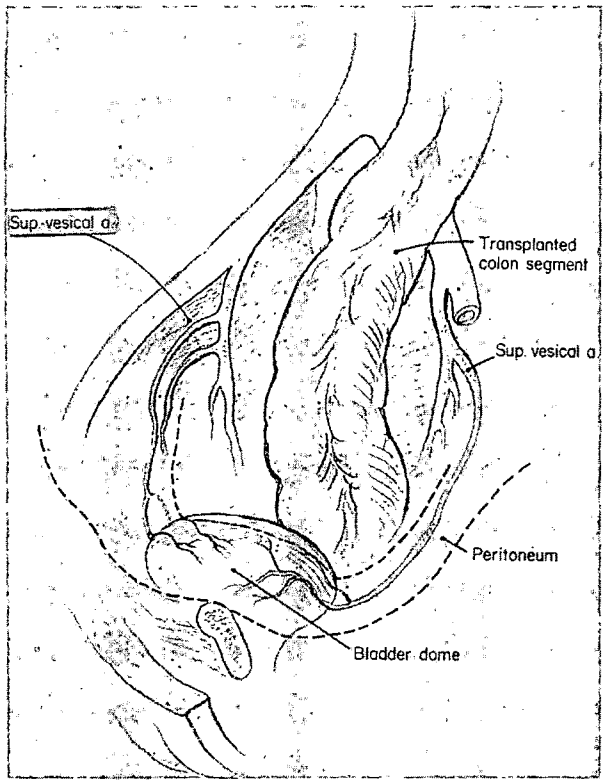


Fig. 2. The reanastomosed transplanted colon segment is noted in the pelvis. The superior vesical artery on either side is shown coursing beneath the pelvic peritoneum and anastomosing in the midline on the bladder dome. The segments of bladder dome and peritoneum to be saved are outlined.

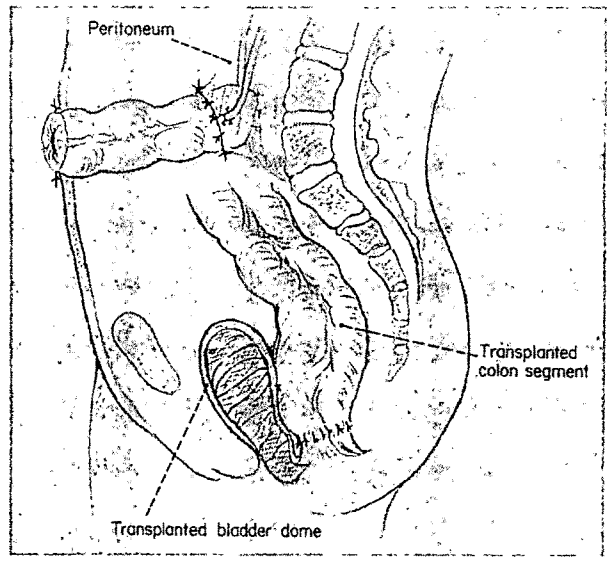


Fig. 3. The urinary conduit stoma is illustrated in the anterior abdominal wall. The anastomosis between the transplanted colon segment and the preserved distal 2 cm. of the anus is represented posteriorly. The transplanted bladder dome has been sutured to the anterior surface of the transplanted colon segment. A split-thickness skin graft is depicted lining the pelvic cavity with a vaginal pack in the neovagina.

urothelium to become infected. The wall of the bladder along with its peritoneal attachments was mobilized, transplanted downward and posteriorly, and then sutured to the anterior wall of the previously transplanted sigmoid colon (Fig. 3). Resection for recurrent pelvic malignancy required that the inferior vesical artery be sacrificed. The superior vesical artery continued to adequately perfuse the remaining fundal segment of the bladder. The anterior wall of the rectum (or transplanted sigmoid colon) formed the posterior wall of the new vagina, and the bladder fundus formed the vaginal apex, as well as the anterior and lateral vaginal walls. It was then possible to reperitonealize the pelvic cavity with the preserved bladder peritoneum. A split thickness skin graft was immediately placed in the newly formed vaginal vault and the vault packed with gauze for 7 days. A vaginal mold created from polyurethane foam was placed in a condom and inserted into the vagina for continued use following discharge from the hospital. The tendency for the neovagina to progressively decrease in size as pelvic fibrosis takes place makes frequent intercourse or continued use of the stent necessary for retention of a functional width and depth.

Three young patients are noteworthy in that they represented especially difficult treatment problems. A 20-year-old patient seen with clinical Stage I vaginal adenocarcinoma associated with intrauterine exposure to diethylstilbestrol (DES) was found upon surgical exploration to have positive para aortic nodes. Following recovery from surgery, she was treated with whole pelvis, para-aortic node, and whole vaginal external radiation therapy. Eighteen months following completion of radiation, the patient developed marked radiation-induced vaginal stenosis. Total vaginectomy and vaginal reconstruction with a split-thickness skin graft was performed with successful restoration of a functional vagina. The patient is currently without known recurrence and is sexually active. A 16-year-old patient with Stage IV DES-related adenocarcinoma of the vagina was treated by external radiation therapy. Incomplete regression of the tumor was observed 10 weeks following completion of therapy. An anterior pelvic exenteration was performed with preservation of a portion of the bladder fundus for vaginal reconstruction. The patient has used a vaginal stent daily and has retained a vagina of functional anatomic depth, although she is not as yet sexually active. A 19-year-old patient with DES-associated Stage I adenocarcinoma of the vagina has required multiple

Table III. Vaginal reconstruction following therapy for gynecologic cancer (1970-1974)

Primary	*No. performed*	*Combined procedures*	*No. performed*
Split-thickness skin graft	3	Skin graft + external pouch	2
External pouch	7	Skin graft + sigmoid	1
Transplanted bladder fundus	4	Skin graft + skin graft	1
Transplanted sigmoid colon	1		4
	23		

reconstruction procedures in order to obtain a functional result. The patient was initially treated by pelvic lymphadenectomy, radical hysterectomy, and total vaginectomy. A split-thickness skin graft was used for vaginal reconstruction at the time of initial surgery. The patient was not active sexually, nor did she regularly use the vaginal stent. As a result of progressive pelvic fibrosis, the depth of the vagina gradually became anatomically inadequate. She subsequently underwent re-excision of the first graft and replacement with a second vaginal skin graft. Since reoperation, she has continued to have an anatomically functional vaginal depth.

Results and comment

Since 1970, vaginal reconstruction has been carried out in 23 patients undergoing extensive treatment for malignant disease (Table IV). Satisfactory vaginal function was achieved in 18 patients. Five patients have not yet been fully evaluated. Three recently underwent surgery and are too early in the course of their treatment for evaluation; one patient recently operated on will require revision before she can be evaluated; and one patient alive with early recurrence has not been sexually active.

Four of 23 patients required two procedures before a functional result was obtained. Split-thickness skin grafts were used as the primary method of reconstruction following total exenteration in two patients where the depth of the vagina was insufficient for function. An external vulvar pouch was subsequently constructed, giving the patients an average vaginal depth of 5 cm.

In one patient with sigmoid substitution in whom the colostomy could not be closed and the fecal stream re-established, the sigmoid colon segment was used as a neovagina by transecting the anterior rectal sphincter at the 12 o'clock position. It was necessary to construct an external vulvar pouch in order to provide needed posterior support.

Three points concerning the rehabilitation of patients who have undergone extensive treatment for pelvic malignancy are of note. First, reconstruction of

Table IV. Vaginal reconstruction following therapy for gynecologic cancer (1970-1974)

Functional vagina		18
Not evaluated		5
Recent surgery	3	
Recent surgery needs revision	1	
Early recurrence	1	

pelvic anatomy is difficult. After pelvic exenteration, surgical reconstruction by means of vaginoplasty and sigmoid pull-through is technically difficult and requires persistence and ingenuity. Following successful restoration of the anatomy, return of total function is not always realized as it is closely related to the motivation and psychological orientation of both the patient and her husband. This is especially true in patients undergoing vaginal reconstruction. The sexual and interpersonal relationships which existed before the onset of the disease are of critical importance in evaluation of the final result obtained. In spite of the complexity of these problems we have found pelvic reconstruction and rehabilitation of these patients to be gratifying. Successful restoration of sexual function and elimination of the need for permanent colostomy has helped selected patients achieve a level of personal and social adjustment which might not otherwise have been possible.

Present surgical techniques are now sufficiently advanced that vaginal reconstruction can be offered to nearly all desiring patients facing loss of sexual function as a result of radiation or surgery for pelvic malignancy. The clinical circumstances encountered are varied and the surgical procedures necessary for optimal reconstruction must be uniquely planned for each patient. If the creation of a new vagina at the time of initial surgery is anticipated, adequate preoperative planning is essential. In this report a new method for internal construction of a vagina was described employing a portion of the anterior bladder fundus. By combining this technique with the sigmoid pull-through procedure, *selected* patients who currently undergo pelvic exenteration may have restoration of both vaginal and rectal function carried out.

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Discussion

DR. DAVID C. FIGGE, Seattle, Washington. One of the more pleasing trends in modern cancer surgery is an increased concern over the ultimate impact of operation on the attitudes and functions of the patient. Laennec suggested that "the object of medicine is the cure of disease." The surgeon today is concerned not only with the ablation of disease, but also with restoring the patient to an acceptable life pattern. Dr. Lagasse's essay is another example of his concern in this direction, and his success in restoring vaginal function in over 75 per cent of instances is a creditable accomplishment.

The majority of the patients presented had had pelvic exenteration. There is but scant information exploring the psychological adjustment following exenteration, but two conclusions seem apparent: The emotional impact of desexualization in such women is a major issue—often even of more significance than the resultant diversion stomas. Yet such patients appear to have a strong potential resilience in returning toward relatively normal functions and activities after the surgical recovery.

Loss of vaginal function is not a problem of concern only to the surgeon. There is abundant evidence that radiation as well can produce dramatic shortening and narrowing of the vagina in up to 80 per cent of women, although preventive measures may reduce this complication. Surprisingly, however, we learn that in many such cases diminished sexual activity may be more directly related to postcoital spotting, dyspareunia, loss of libido, fear of recurrent cancer, and changes in attitude by the husband. One is left with the impression that satisfactory coital function is far more complex an issue than merely the formation or preservation of a measurably satisfactory vaginal tube. Surgeons often have a tendency to think in terms of anatomic structure in contrast to function and if one can extrapolate the observations following radiation it provokes a thoughtful concern that Dr. Lagasse's success in reconstructing an anatomically suitable vaginal canal might reach only the tip of the iceberg of successful function. Unless synchronous and expert pre- and postoperative psychological guidance of such patients parallels the surgical procedure, much of the full advantage of such an effort may not be forthcoming. Dr. Lagasse and his co-workers are, of course, quite appreciative of this aspect.

The paper today has dwelt at length on the technical aspects of the four described methods of vaginal reconstruction and has emphasized that no one method is completely satisfactory. In our own cases, we have developed a preference for the Williams method of construction of the vulvovaginal pouch. We were initially impressed with this procedure as an adjunct to the Frank technique of pressure indentation in cases of vaginal agenesis and felt the resultant vagina represented an improvement over the traditional McIndoe procedure. The advantages are significant and particularly relevant to the postexenteration patient. The operative procedure is simple, the hospital time dramatically shortened, the need for long-term dilatations and stents is obviated. The resultant vaginal canal is supple and flexible, it provides good clitoral stimulation with coitus and the problems of fibrosis and secondary shortening or constriction are eliminated. Our patients have been satisfied with the result. Curiously, several women have requested the procedure following exenteration and have felt it was of supportive help in re-establishing their self-esteem, although they anticipated no sexual encounters in the future. It appeared a critical step in re-establishing

their personal image and in offsetting the desexualizing nature of the primary surgery.

One must again commend Dr. Lagasse and his co-workers for enlarging their interests beyond the immediate scope of cancer control. Just as the oncologist must be conversant with the many avenues of cancer therapy, he must also be cognizant and sympathetic toward the total impact of the disease and its implied therapy on the life style, personal image, and emotional adjustments of the patient he treats.

DR. RAPHAEL B. DURFEE, Portland, Oregon. We have treated four young women, all in their teens or early twenties, for rhabdomyosarcoma by radial hysterectomy and partial vaginectomy. Of the four, three have survived for 5 years and the fourth died after 4 years. In each instance, a modification of the Frank technique was used to create a neovagina in which the operated area of the upper vagina was opened up and an Evans mold was placed to hold it open. No skin graft was used since the mucosa which was present was easily induced to produce epithelization upward of the new canal. Local estrogen cream was used for this purpose. This is another effective way to solve the problem of creating a neovagina. It is obviously not possible to use estrogen stimulation, even locally, in this area if the previous tumor were estrogen sensitive. If the vaginal mold is worn for at least a year, a deep, functional, well-epithelized vagina will result.

DR. LAGASSE (Closing). I think oncologists in the future will be able to give more consideration to reconstruction and rehabilitation, but until recently morbidity and death from any oncologic procedures were too high to allow this "luxury." It is only since results have improved that we have been able to begin to think creatively about reconstructive procedures.

I would commend the Williams procedure for consideration, because it is simple and the results are quite satisfactory.

Primary carcinoma of the Fallopian tube

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A series of 26 unreported cases of primary carcinoma of the Fallopian tube is presented. These cases were collected from seven hospitals in Portland, Oregon, for a period of 10 years, i.e., from 1963 to 1974. No statistical data can be made except to state that seven patients of the 26 are known to be alive and well. Of these seven living patients, two have been followed for over 5 years and five have been followed for over 2 years. All are free of disease at the present time. Three other patients lived over 5 years but finally died of their disease. All of these patients were in the Stage I category except two who were in the Stage II category. This suggests that any breakthrough of the serosa of the Fallopian tube is an ominous sign with poor prognosis. The need for earlier diagnosis and supplementary therapy for Stage II of this disease is discussed.

THE PURPOSE of this paper is to report 26 unreported cases of primary carcinoma of the Fallopian tube. The cases were collected from seven different institutions within the metropolitan area of Portland, Oregon. Cases were selected by criteria of Finn and Javert.[1]

The rarity and gravidity of this tumor is well known. The incidence of carcinoma of the Fallopian tube varies from 0.15 per cent[2] to 1.8 per cent[3] of all primary malignancies in the genital tract.

The classic first reported case was that of Orthmann[4] in Germany in 1886.

Less than 1,000 cases of primary carcinoma of the Fallopian tube have been reported in the literature to date. There were 780 cases collected in 1965 by Jones[3] and about 20 new lesions are reported yearly.

Results and comments

The highest age incidence in this series of carcinoma of the Fallopian tube was between 50 and 70 years (Table I). Only seven (20 per cent) were under the age of 50 years. The youngest patient was 33 years of age and the oldest was 80. The mean average age in this series was 58 years. This is an older age group than Sedlis'[5] large series of 230 collected cases; the average age of those patients was 52.

Bilateral involvement in primary carcinoma of the Fallopian tube has been mentioned by almost all investigators. Sedlis[5] in his series placed bilateral involvement at 26 per cent. Bilateral involvement in the present series was two of 26 (8 per cent).

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Carcinoma of the Fallopian tube, like carcinoma of the ovary, is often asymptomatic. It is often discovered by finding a pelvic mass or by irregular intermenstrual or postmenstrual bleeding. About 50 per cent of the patients had abdominal pain of a nonspecific character, such as intestinal cramping, dysmenorrhea, or intestinal obstruction symptoms. Watery discharge, occasionally blood-tinged, is also a common symptom. Hydrops tubae profluens is a syndrome which is characterized by colicky pain in the lower abdomen relieved by a profuse, serous, watery, yellow, intermittent discharge from the vagina. It is thought to be a filling and emptying of a partially blocked Fallopian tube. This is the classical diagnostic hallmark of carcinoma of the Fallopian tube. Unfortunately, it is absent in most cases. In our series of 26, it occurred in only three cases. Vaginal bleeding occurred in about 35 per cent of the cases, and pain in 28 per cent.

The preoperative findings were masses in the adnexa in eight cases (29 per cent) and nodules in the cul-de-sac in four (14 per cent). Two had distention of the abdomen. Some had urinary symptoms and some had no symptoms whatsoever. The preoperative diagnoses were benign or malignant neoplasia, uterine myoma, endometriosis, and pelvic inflammatory disease. One was diagnosed preoperatively by laparoscopy.

Of the 26 cases reviewed, eight had had previous gynecologic surgery. Only three of these cases were significant. One patient had a vaginal hysterectomy for prolapse of the uterus and a small fragment of the tube was noted by the gynecologist to be abnormal. The pathologist was requested after the routine sections to recut this area and a primary carcinoma of the Fallopian tube was found. A laparotomy several weeks later was done and the opposite tube was removed and

found to be normal. She is still alive 2½ years later. The other two cases that deserve mention were those in which two normal curettages for malignancies were performed but the patients continued to bleed and subsequent surgery revealed tubal carcinoma.

Although one would expect the Papanicolaou smear to aid in diagnosis of this malignancy, we did not find this true. The sedimentation rate, an often neglected laboratory aid, was elevated in all the cases in which it was done. It ranged from 25 to 75 mm. per hour.

In this series, 20 of the 26 patients had total abdominal hysterectomy and bilateral salpingo-oophorectomy. Of the remaining six, one had a vaginal hysterectomy and a unilateral salpingo-oophorectomy, and a subsequent abdominal operation in which the remaining ovary and tube were removed. Two patients had biopsies and closure. The remaining three patients had one or both tubes removed. These three patients had had, as in other series, previous gynecologic surgery.

It was almost routine in the Stage I cases to use prophylactic irradiation, i.e., external cobalt orthovoltage, or the linear accelerator, and, in addition, radioactive colloidal chromic phosphate (^{32}P) (see Table I).

It was also almost routine to use a course of external irradiation for the Stages II and III patients. It is admitted that the quality of irradiation, i.e., orthovoltage, supravoltage, or megalovoltage, was quite variable and it is difficult to compare the results. The patients in this group often had far-advanced disease. Because of the high incidence of bowel complications following postoperative external irradiation, individualization of treatment should be exercised.

Summary of clinical data of 26 cases of carcinoma of the Fallopian tube

There are seven known living survivors of the 26 patients studied with primary carcinoma of the Fallopian tube (case 2 to 8). No statistical data can be made as only seven patients have been followed for more than 2 years. Of these seven cases, only two patients (cases 2 and 3) have lived longer than 5 years. All of these seven patients are alive and well and apparently free of their disease at the present time.

Of these seven, five had total abdominal hysterectomy and a bilateral salpingo-oophorectomy. One had bilateral salpingo-oophorectomy 6 years after vaginal hysterectomy, and one had left salpingo-oophorectomy several weeks after vaginal hysterectomy and right salpingo-oophorectomy (Table I).

All staging, by necessity, was done at the time of surgery and was not preoperative (see Table I). The clinical staging in these cases was that of Erez and associates.[6] I concur with their experience and our findings that carcinoma of the Fallopian tube was by contiguous growth through the tube to the serosa, and then the dominant spread is by surface metastasis. We had only three cases which spread to near or distant lymph nodes. We used the grading classification of Hu and associates.[7] We attempted to use this classification as closely as possible with the information available to us. The study showed that there was only one Stage I in the 18 deceased patients. This fact agrees with the finding of Schiller and Silverberg[8] that extension of the tumor to the serosa of the Fallopian tube is indeed an ominous finding. Both of our patients with bilateral tubal involvement are alive and well, but have been followed for only a little over 2 years.

In this survivor group of seven patients, four had supplementary postoperative cobalt-60 therapy, three of whom had additional ^{32}p (radioactive chromic phosphate) shortly after their surgery, and one had irradiation from a linear accelerator source. All had palpable abdominal masses without ascites, and one was diagnosed preoperatively by laparoscopy.

Eighteen patients are known to be dead (cases 9 to 18). Only two of the patients (cases 9 and 10) lived longer than 5 years, and both died of carcinoma of the Fallopian tube. There were only two Stage I cases of these 18 deceased patients (see Table I).

In the 16 cases in which irradiation was used, six had small bowel obstructions. One bowel obstruction occurred in one of the seven "living and well" patient group. One irradiated patient developed a myxoliposarcoma of the abdominal wall. Chemotherapy was not used to any extent, except in isolated cases. For example, a progestin, medroxyprogesterone (Colprone), chlorambucil (Leukeran), 5-fluorouracil, mephalan (Alkeran), cyclophosphamide (Cytoxan), and vincristine (Oncovin) (see Table I).

The extent of the disease found at the time of surgery seems to be the most important survival factor. A more comprehensive staging classification suggested by Schiller and Silverberg[8] is based on a detailed microscopic study of the wall of the Fallopian tube. This lack of comprehensive pathologic staging and the lack of guidelines for irradiation and chemotherapy form an argument for establishing a center for analyzing and computerizing the data for this rare tumor. This would be far better than studying the isolated cases, which is being done at the present time.

The fact still remains that the disease limited to within the Fallopian tube, i.e., Stage I, does well with adequate surgery and with no other therapy, and that patients with carcinoma found to be Stage III or IV have a life expectancy of less than 2 years. Therefore, carcinoma involving the Fallopian tube which has infiltrated to surrounding pelvic structures, Stage II, needs more study as to adequate therapy.

Table I. Primary carcinoma of Fallopian tube: Summary of clinical data*

No.	*Age*	*Parity*	*Stage*	*Grade*	*Findings at surgery*	*Treatment*	*Chemotherapy radiation*	*Follow-up*
1.	59	?	I	I	Papillary Ca. of right Fallopian tube. Mass in adnexa	TAH-BSO	Chlorambucil, deep x-ray 1972	Papillary transitional cell Ca. of bladder after 11 yr. A & W 1972
2.	48	III	I	II	Adenocarcinoma of right Fallopian tube. Adnexal mass, fibroids, endometriosis	TAH-BSO	No, only Colprone	A & W 7 yr.
3.	43	III	I	I	Papillary Ca. of right Fallopian tube. Adnexal mass, previous vaginal hysterectomy	BSO	Cobalt-60 + ^{32}P	A & W 7 yr.
4.	52	?	I	II	Adenocarcinoma of right Fallopian tube. Uterine fibromyomas	Vag. hyst., RSO. Later, LSO.	Cobalt-60	A & W 3½ yr. bowel obstruction
5.	60	V	I	II	Bilateral adenocarcinoma of Fallopian tubes. Bilateral mass, fibroid uterus, fibroma of ovaries	TAH-BSO	Linear accelerator, 4,950 rads	A & W 2½ yr.
6.	61	I	II	II	Adenocarcinoma of right Fallopian tube. Right adnexal mass, laparoscopy	TAH-BSO	Cobalt-60 + ^{32}P	A & W 2 yr.
7.	33	II	I	I	Bilateral papillary Ca. of Fallopian tubes. Bilateral swollen tubes, endometriosis in cul-de-sac	TAH-BSO	No	A & W 2 yr.
8.	60	I	I	III	Carcinoma of right Fallopian tube. Adnexal mass	TAH-BSO	Cobalt-60 4,050 rads, ^{32}P	A & W 2 yr.
9.	52	?	I	II	Adenocarcinoma of right Fallopian tube. Cystic benign lesion of ovary, right adnexal mass	TAH-BSO	Chlorambucil, cobalt-60	Dead 8 yr. of Ca. of Fallopian tube
10.	47	III	II	III	Adenocarcinoma of left Fallopian tube. 10 cm. adnexal mass	TAH-BSO	5-FU	Dead 7 yr. ascites, Ca. of Fallopian tube
11.	54	III	III	II	Adenocarcinoma of right Fallopian tube	TAH-BSO	Cobalt-60 4,000 rads	Dead 1 yr. Ca. of Fallopian tubes, pleural effusion
12.	67	I	II	III	Adenocarcinoma of left Fallopian tube, 13/2.5 cm. mass, omentectomy	TAH-BSO	Cobalt-60 5,000 rads, Cytoxan	Dead 4 yr. 5 mo. small bowel fistula from adenocarcinoma of Fallopian tube
13.	80	?	II	III	Carcinoma of right Fallopian tube. 8 cm. right adnexal mass	TAH-BSO	Cytoxan ^{32}P "radiation"	Dead 4 yr. 2 mo. of disease, abdominal distention
14.	69	II	II	II	Papillary adenocarcinoma of left Fallopian tube. Adnexal mass, abdominal hysterectomy, 1963	BSO	Cobalt	Dead 3 yr. myxoliposarcoma of abdominal wall, ascites
15.	73	?	II	II	Adenocarcinoma of right Fallopian tube. Right adnexal mass, hematosalpinx	TAH-BSO	Intracavitary radium	Dead 1½ yr. of disease
16.	61	I	I	II	Papillary Ca. of left Fallopian tube. Chronic salpingitis, soft mass, left	TAH-BSO	No	Dead. Last visit 1966, less than 1 yr. Died of disease
17.	77	III	III	II	Adenocarcinoma of right Fallopian tube. Suprapubic mass (abscess)	RSO, prev. hyst. at 41	^{32}P orthovoltage 4,000 rads	Dead 10 mo. of ileus and distention
18.	69	II	III	II	Papillary adenocarcinoma of left Fallopian tube. Enlarged left Fallopian tube, inguinal lymph nodes	TAH-BSO, omentectomy	^{32}P orthovoltage 4,000 rads to abdomen, 5,000 rads right inguinal region	Dead 8 mo. of disease
19.	61	?	IV	II	Carcinoma right Fallopian tube. Supraclavicular node in neck, mass, PID	TAH-BSO	Cobalt	Dead after 8 mo. of advanced disease

*TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RSO, right salpingo-oophorectomy; 5-FU, 5-fluorouracil; A & W, alive and well.

Table I. cont'd.

No.	*Age*	*Parity*	*Stage*	*Grade*	*Findings at surgery*	*Treatment*	*Chemo-therapy radiation*	*Follow-up*
20.	55	?	III	III	Carcinoma of right Fallopian tube. 3 mo. pregnant size, pelvic mass, "fibroids"	TAH-BSO	"Deep x-ray"	Dead after 7 mo. carcinomatosis, bowel obstruction
21.	53	III	IV	III	Carcinoma of left Fallopian tube. Pelvic nodes, bilateral salpingitis	Carcinomatous, no specimen	Cobalt	Dead 5 mo. of disease
22.	55	0	III	II	Carcinoma right Fallopian tube. Cervical stenosis, distended abdomen, ascites	TAH-BSO	No	Dead 2 mo. of disease
23.	64	?	III	III	Right Fallopian tube ascites carcinomatous	Biopsy	No	Dead 2 mo. of disease
24.	66	III	III	I	Carcinoma of left Fallopian tube. Large pelvic mass. Metastases to omentum	TAH-BSO	5-FU, Vincristine, ^{32}P 5,000 rads	Presumed dead, no follow-up
25.	42	I	III	II	Carcinoma of left Fallopian tube. Mass left adnexa carcinomatous, TAH 1960	BSO and omentectomy	No	Presumed dead, metastases to vagina
26.	62	0	III	II	Carcinoma of left Fallopian tube. Cystic mass, left—size of grapefruit, carcinomatous	TAH-BSO	No	Presumed dead, ascites

Repeated negative Gravlee washes, or a negative curettage for malignancy, in the presence of continued vaginal bleeding should alert one to the possibility of carcinoma of the Fallopian tube in a woman 45 years or older. Bilateral tumors in Schiller and Silverberg's[8] cases had a 21 per cent incidence. Bilateral tumors are generally ascribed to development of separate malignancies, and no prognostic significance has been noted; however, Schiller and Silverberg felt that bilaterality indicated a more advanced disease. The survival rate did not differ from that of patients with other comparable unilateral tumors of similar stage.

Phelps and Chapman's[9] recent paper on supplementary irradiation therapy in primary carcinoma of the Fallopian tubes reported good results for those patients whose disease is limited to the pelvis, i.e., Stages I and Stage II. They employed a 1,000,000 volt resonant transformer apparatus (General Electric) and in subsequent years a 25 MeV. betatron (Allison Chalmers) or a 4 MeV. linear accelerator (Varian).

They treated four Stage I cases; three of these patients are alive and well over 5 years and one died in 5 months. They had five Stage II patients who are alive and well from 1½ to 16 years (three are 5 year survivors). All Stage III patients did not survive. When it was technically feasible radioactive colloid (^{198}Au or ^{32}P) was instilled into the peritoneal cavity.

All authors agree that total abdominal hysterectomy with a bilateral salpingo-oophorectomy with removal of all large tumor masses is essential. This includes careful staging for future irradiation or chemotherapy.

With the use of chemotherapy in the late 1960's, more attempts with multiple chemotherapeutic agents are being used in genital malignancies. The use of chemotherapy in conjunction with irradiation is being explored, not only in uterine and ovarian carcinoma, but also in this disease as well. At the present time, should the criteria for chemotherapy for the Fallopian tubes be the same as for uterine cancer since they come from the anlage? In this small series, progestins were only rarely used. Alkalating and other chemotherapeutic agents were only occasionally used. The use of progestins for carcinoma of the uterine tubes was based on the work of Kistner and associates[10] of inhibiting neoplasia of the endometrium. We also like the drug because it has so few adverse side effects.

The early use of the laparoscope in a postmenopausal palpable adnexal mass and the use of the total body EMI (computerized axial tomography) may aid the gynecologist in earlier diagnosis of this disease, and subsequently improve its present dismal prognosis.

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Discussion

DR. GLEN E. HAYDEN, Seattle, Washington. Dr. Kinzel has made a valuable contribution with his paper outlining these unreported cases of primary carcinoma of the Fallopian tube. He has presented problems of diagnosis, management, and survival rates.

Since our ability to make early diagnoses is at best limited, it is hoped that with the assistance of the laparoscope we may be more successful. However, the laparoscope is not capable of seeing within the Fallopian tube. The symptomatology, age, and previous pregnancy patterns are not unlike those of all other series that have been reported. Unfortunately, the staging and therapy are widely diversified and no single program has been developed, except that surgery is the definitive method of therapy.

From the Chicago Lying-in Hospital, a series of 12 patients was reported by Hayden and Potter.[1] Ten of the cases demonstrated gross and microscopic evidence of chronic inflammation. A second series, which I have had the opportunity of reviewing, consisted of 15 cases from the Virginia Mason Medical Center Cancer Registry. There were three patients with the diagnosis of definite inflammation. The survival rates of both series achieve the universal average of 27 per cent for more than 5 years. Of the 27 cases from the combined Chicago Lying-in and Virginia Mason Series, the modality of therapy varied to such an extent that no uniform recommendation could be made. In the extensive lesions, more often than not we approached and diagnosed the problem as ovarian carcinoma, and probably should do so on the basis that the metastatic process is similar. As yet, the electronmicroscopist is unable to differentiate ovarian from Fallopian tube carcinoma. Microscopically, as seen in the Chicago Lying-In Series, tube process tends to involve the entire mucosal surface extending the length of the Fallopian tube. Of added interest was the reported case of carcinoma in situ in one patient.

The laparoscope may offer us the ability for earlier diagnosis in the patient with questionable pelvic pain and/or suspect adnexal masses of tube or ovary. Thereby, an earlier diagnosis may occur with eventually better results. Dr. Kinzel wisely has recommended that a central registry would be of invaluable assistance to acquire a larger amount of data more rapidly.

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DR. J. PAUL SHIVELY, San Francisco, California. I have had two cases of primary adenocarcinoma of the Fallopian tube. I believe that Dr. Lou Emge reported six cases of carcinoma of the Fallopian tube in 1948. His longest survival was 18 months.

In 1953 I had a 48-year-old patient with a positive pap smear. I then did a D&C and biopsy of the cervix and they were reported negative. Because of honey-colored discharge and a positive Pap smear, I then did a total abdominal hysterectomy and a bilateral salpingo-oophorectomy. Following that she had an uneventful recovery for 2 months and then developed an abdominal mass with ascites. Dr. Edward Hill did a paracentesis which was positive for malignant cells.

She was then given external radiation. The ascites and the abdominal mass disappeared. Then something else happened. I submit she had some sort of self-immunization much like vaccination to her tumor.

It is now 22 years later and she is alive and well. She speaks only Spanish and I speak only English but we do communicate somehow. I had little to do with her recovery except that I did the surgery, because her host immune response was amazing.

I also had one other patient with a primary carcinoma of the Fallopian tube who survived 2½ years.

DR. KINZEL (closing). I thought that Dr. Hayden was very kind in his discussion. He is right when he said this disease is hard to diagnose.

I think if we are going to increase the survival rate of both ovarian and Fallopian tube malignancies, we are going to have to be more aggressive in making an early diagnosis. My experience was that any patient with a Fallopian neoplasm beyond a Stage I didn't last much longer than 2 years.

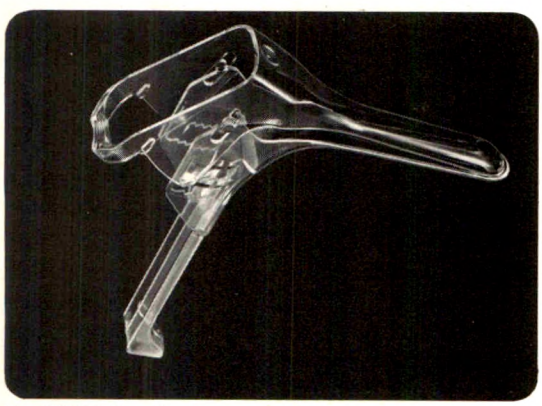
There are some interesting survival figures in 1975 by Phelps and Chapman with good survival rates of cases of Stage II with irradiation and chemotherapy.

Therapy in this disease is still in a state of flux.

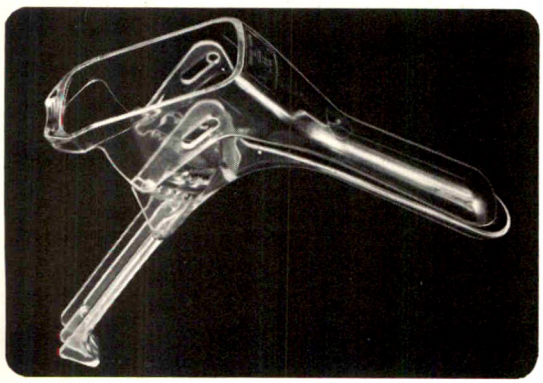
I wish to compliment Dr. Shively on having two patients, one of whom had ascitic fluid and a 22 year survival.



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The woman profiled here is an actual ZORANE 1/50 user. However, not all women can be expected to have the same tolerance for side effects, should any occur. (Data on file, Lederle Laboratories)

*Dropout rates are based on total patient population (1,156); incidence reflects only those patients who completed one or more cycles (956).

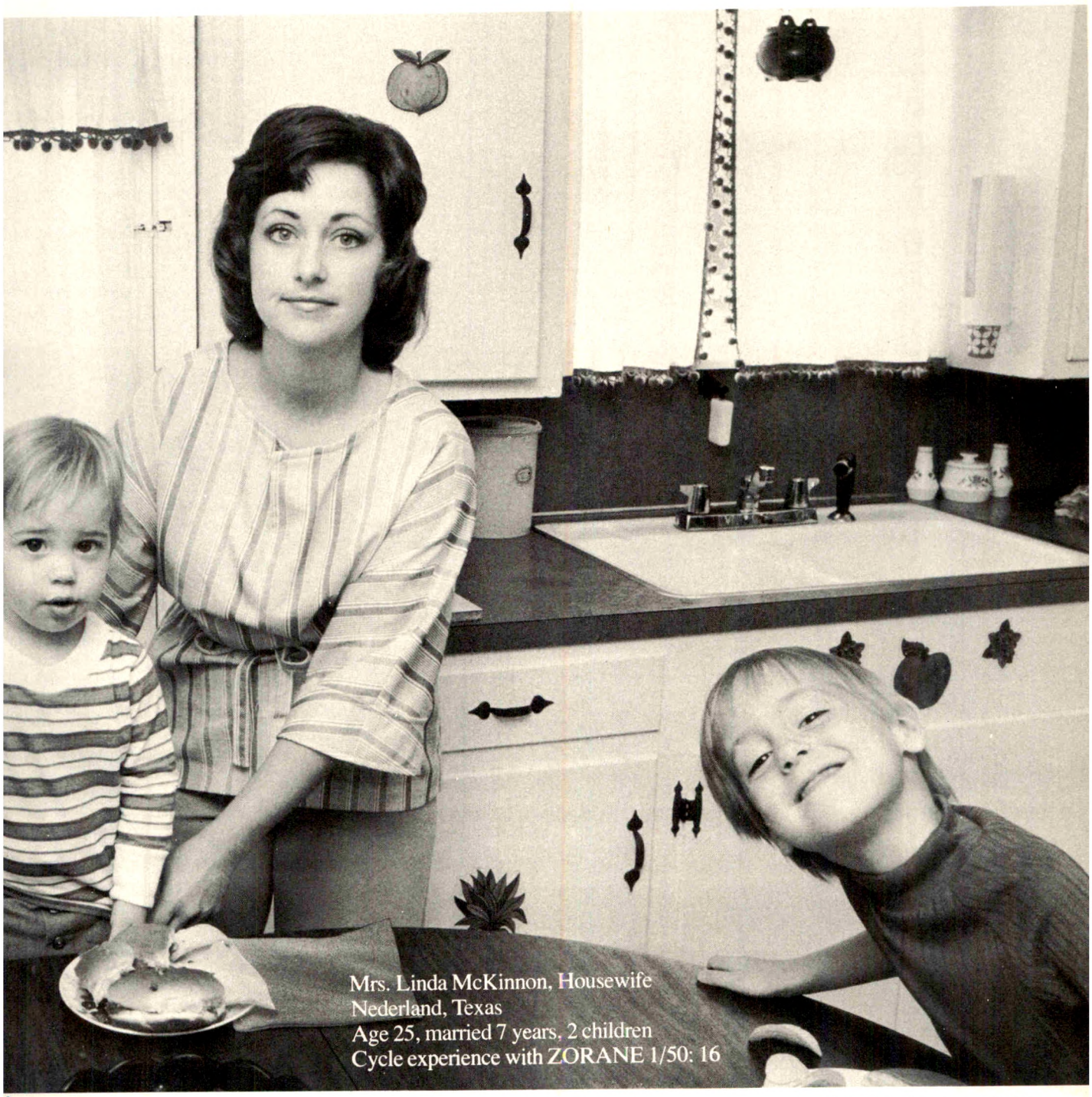
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Zorane 1/20 Norethindrone Acetate, 1 mg. and Ethinyl Estradiol, 20 mcg.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of sequential products appears to be somewhat lower than that of combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons, as observed in clinical trials, with ZORANE 1.5/30 appears to be the same as that of higher dose combination products. The dropout rate due to irregular bleeding was somewhat higher, but dropouts were equally split between irregular bleeding and other medical reasons attributable to the drug. (ZORANE 1/20 only: The effectiveness is somewhat lower than that of the higher dose combination products. Both provide almost completely effective contraception. Dropout rate for medical reasons appears to be somewhat higher than with higher dose combination products, due particularly to irregular bleeding.) An increased risk of thromboembolic disease associated with use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, reduced tolerance to carbohydrates, have not been quantitated with precision. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. Possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indications: For control of conception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen-dependent neoplasia; undiagnosed abnormal genital bleeding; pregnancy.

Warnings: If early signs of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis) occur or are suspected, discontinue use of drug immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug stoppage and not enhanced by long-term use.[1-4]) If sudden partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Safety of use in pregnancy has not been established, therefore rule out pregnancy in any patient who has missed two consecutive periods before continuing contraceptive regimen; if prescribed schedule has not been adhered to, consider possibility of pregnancy with first missed period. A small fraction of hormonal agents has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant has not yet been determined.

Precautions: Pretreatment and periodic physical examinations of breasts and pelvic organs should include Papanicolaou smear. (Estrogens have produced tumors, some malignant, in 5 species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after drug withdrawal for 2 months. With use of these drugs, pre-existing uterine fibromyomata may increase in size; and some conditions (*i.e.*, epilepsy, migraine, asthma, cardiac or renal dysfunction) may be influenced by fluid retention; observe carefully for such. With use of ZORANE 1.5/30 or ZORANE 1/20, alteration in menstrual patterns may be induced. Since the amount and duration of flow and cycle length may vary, this must be considered in attempting to determine if cause of bleeding is organic. (ZORANE 1/50 only: In breakthrough bleeding or all cases of irregular bleeding per vaginam, keep in mind nonfunctional causes and take adequate diagnostic measures.) With history of psychic depression, discontinue drug if depression recurs to a serious degree. Possible influence of prolonged ZORANE therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been seen in some patients on oral contraceptives; carefully observe diabetics on such therapy. Patient age is no absolute limiting factor, although these drugs may mask onset of climacteric. The pathologist should be advised of ZORANE therapy when relevant specimens are submitted. Susceptible women may have an increase in blood pressure following use of contraceptive steroids.

Adverse Reactions Observed in Patients Receiving Contraceptives: Statistically significant association demonstrated between use of oral contraceptives and: thrombophlebitis pulmonary embolism, cerebral thrombosis. Suggestive evidence, neither confirmed nor refuted between use and neuro-ocular lesions (*e.g.* retinal thrombosis, optic neuritis). Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps, bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema chloasma or melasma, breast changes (tenderness, enlargement, secretion), weight change (increase or decrease), changes in cervical erosion and secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible women, mental depression. Reported association with use, neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching. *May Alter Laboratory Results in:* hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX, X), thyroid function (increase in PBI_1, and butanol extractable protein bound iodine, and decrease in T^3 uptake values), metyrapone test, pregnanediol determination.

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T. H. Lippert, P. B. De Grandi, and R. Fridrich
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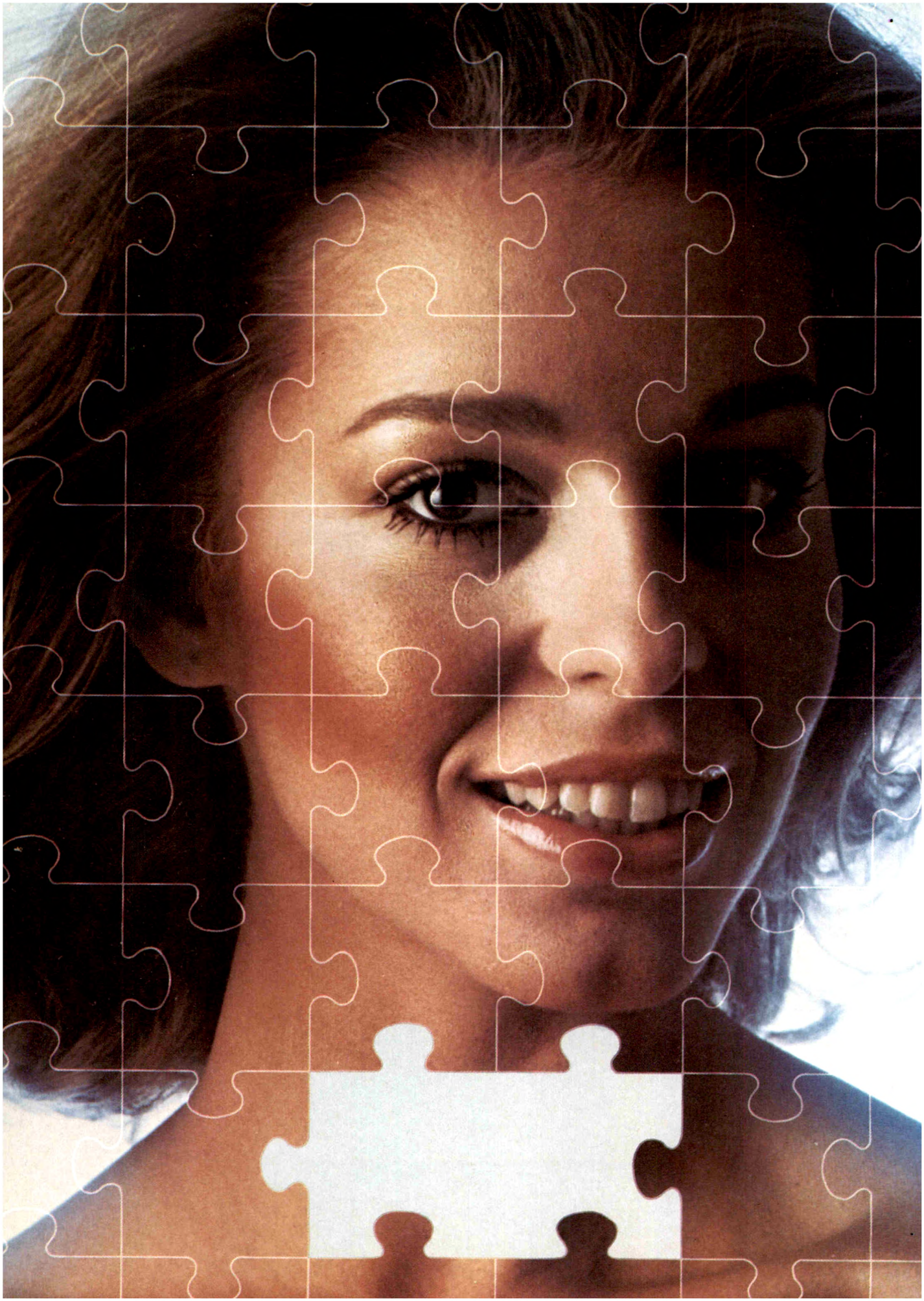
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1. Stock, J. M., Surks, M. I., and Oppenheimer, J. H. Replacement dosage of L-thyroxine in hypothyroidism. A re-evaluation. New Engl. J. Med. 290:529-33, 1974.

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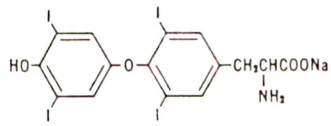
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Both SYNTHROID products will provide L-thyroxine as a substrate for physiologic deiodination to L-triiodothyronine. Therefore, patients taking SYNTHROID products will demonstrate normal blood levels of L-triiodothyronine even when the thyroid gland has been surgically removed or destroyed by radioiodine. Administration of levothyroxine alone will result in complete physiologic thyroid replacement.

Indications: SYNTHROID (sodium levothyroxine) products serve as specific replacement therapy for reduced or absent thyroid function of any etiology. SYNTHROID **Injection** can be used intravenously whenever a rapid onset of effect is critical, and either intravenously or intramuscularly in hypothyroid patients whenever the oral route is precluded for long periods of time.

Contraindications: There are no absolute contraindications to SYNTHROID (sodium levothyroxine) therapy. Relative contraindications include acute myocardial infarction, uncorrected adrenal insufficiency and thyrotoxicosis. (See WARNINGS)

Warnings: Patients with cardiovascular diseases warrant particularly close attention during the restoration of normal thyroid function by any thyroid drug. In such cases, low initial dosage increased slowly by small increments is indicated. Occasionally, the cardiovascular capacity of the patient is so compromised that the metabolic demands of the normal thyroid state cannot be met. Clinical judgment will then dictate either a less-than-complete restoration of thyroid status or reduction in thyroid dosage.

Endocrine disorders such as diabetes mellitus, adrenal insufficiency (Addison's disease), hypopituitarism and diabetes insipidus are characterized by signs and symptoms which may be diminished in severity or obscured by hypothyroidism. SYNTHROID (sodium levothyroxine) therapy for such patients may aggravate the intensity of previously obscured symptoms and require appropriate adjustment of therapeutic measures directed at these concomitant disorders.

Thyroid replacement may potentiate the effects of anticoagulants. Patients on anticoagulant therapy should have frequent prothrombin determinations when instituting thyroid replacement to gauge the need to reduce anticoagulant dosage.

Precautions: Overdosage with any thyroid drug may produce the signs and symptoms of thyrotoxicosis, but resistance to such factitious thyrotoxicosis is the general rule. With SYNTHROID (sodium levothyroxine) **Tablets,** the relatively slow onset of action minimizes the risk of overdose but close observation in the weeks following institution of a dosage regimen is advised. Treatment of thyroid hyperactivity induced by oral medication is confined to interruption of therapy for a week, followed by reinstitution of daily therapy at an appropriately reduced dosage.

Adverse reactions: Adverse reactions are due to overdose and are those of induced hyperthyroidism.

Dosage and administration: For most adults, a final dosage of 100 mcg (0.1 mg) to 200 mcg (0.2 mg) of SYNTHROID (sodium levothyroxine) **Tablets** daily will restore normal thyroid function and only occasionally will patients require larger doses. Failure to respond adequately to a daily oral intake of 400 mcg (0.4 mg) or more is rare and should prompt reconsideration of the diagnosis of hypothyroidism, special investigation of the patient in terms of malabsorption of L-thyroxine from the gastrointestinal tract or poor adherence to therapy.

The concomitant appearance of other diseases, especially cardiovascular diseases, usually dictates a replacement regimen with initial doses smaller than 100 mcg/day (0.1 mg).

In otherwise healthy adults with relatively recent or of hypothyroidism, full replacement dose of 150 mc (0.15 mg) or 200 mcg (0.2 mg) has been instituted immediately without untoward effect and with good therapeutic response. General experience, however, favors a more cautious approach in view the possible presence of subclinical disorders of the cardiovascular system or endocrinopathies.

The age and general physical condition of the patie as well as the severity and duration of hypothyroid symptoms determine the starting dosage and the rate of incremental dosage increase leading to a final maintenance dosage. In the elderly patient with long standing disease, evidence of myxedemat infiltration and symptomatic, functional or electrocardiographic evidence of cardiovascular dysfunction, the starting dose may be as little as 25 n (0.025 mg) per day. Further incremental increases of 25 mcg (0.025 mg) per day may be instituted at th to four week intervals depending on patient response. Conversely, otherwise healthy adults ma be started at higher daily dosage and raised to the full replacement dosage in two to three weeks. Clearly it is the physician's judgment of the severity of the disease and close observation of patient response which determines the rate of dosage titration.

Laboratory tests to monitor thyroid replacement therapy are of limited value. Although measuremen of normal blood levels of thyroxine in patients on replacement regimens frequently coincides with clinical impression of normal thyroid status, higher than normal levels on oral replacement of levothyroxine occasionally occur and should not b considered evidence of overdosage per se.

In all cases, clinical impression of the well-being of patient takes precedence over laboratory determination in determining the appropriate individual dosage.

In infants and children, there is a great urgency to achieve full thyroid replacement because of the criti importance of thyroid hormone in sustaining growth and maturation. Despite the smaller body s the dosage needed to sustain a full rate of growth, development and general thriving is higher in the child than in the adult, as much as 300 mcg (0.3 mg) to 400 mcg (0.4 mg) per day.

In myxedema coma or stupor, without concomitant severe heart disease, 200 to 500 mcg of SYNTHRO **Injection** may be administered intravenously as a solution containing 100 mcg/ml. Although the patient may show evidence of increased responsivity within six to eight hours, full therapeutic effect may not be evident until the following day. An additional 100 to 300 mcg or more may be given on the second day if evidence of significant and progressive improvement has not occurred. Like the oral dosage form, SYNTHROID **Injection** produces a predictable increase in the circulating level of hormone with a long half-time. This usually precludes the need for multiple injections but continued daily administration of lesser amounts intravenously should be maintained until the patier fully capable of accepting a daily oral dose.

In the presence of concomitant heart disease, the sudden administration of such large doses of L-thyroxine intravenously is clearly not without its cardiovascular risks. Under such circumstances intravenous therapy should not be undertaken without weighing the alternative risks of the myxedema coma and the cardiovascular disease. Clinical judgment in this situation may dictate smaller intravenous doses of levothyroxine.

SYNTHROID **Injection** by intravenous or intramusc routes can be substituted for the oral dosage form when ingestion of SYNTHROID **Tablets** is precluded for long periods of time.

How Supplied: SYNTHROID (sodium levothyroxine **Tablets** are supplied as scored, color-coded compres tablets in 6 concentrations: 25 mcg (0.025 mg)—orar . . . 50 mcg (0.05 mg)—white . . . 100 mcg (0.1 mg) yellow . . . 150 mcg (0.15 mg)—blue . . . 200 mcg (0.2 mg)—pink . . . 300 mcg (0.3 mg)—green.

SYNTHROID (sodium levothyroxine) for **Injection** i supplied in 10 ml vials containing 500 mcg of lyophilized active ingredient and 10 mg of Mannito U.S.P. A separate 5 ml vial containing Sodium Chloride Injection, U.S.P. is provided as a diluent.

Directions for reconstitution: Reconstitute the lyophilized sodium levothyroxine by aseptically add 5 ml of the Sodium Chloride Injection, U.S.P. to the vial. Shake vial to insure complete mixing. **U immediately** after reconstitution. Discard any unused portion.

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Actions: ORTHO-NOVUM 1/50 ☐21 and ORTHO-NOVUM 1/50 ☐28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/50 ☐21 and ORTHO-NOVUM 1/50 ☐28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesion should be considered if the patient has abdominal pain or evidence of intra-abdominal blee ing. This has been reported in short-term as well as long-term users of oral contraceptives

Precautions: 1. A thorough history and physical examination should be performed befo prescribing oral contraceptives and periodically during their administration and should includ special reference to breasts and pelvic organs, including Papanicolaou smear since estroge have been known to produce tumors, some of them malignant, in five species of subprima animals. 2. Endocrine and possibly liver function tests may be affected by treatment wi ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28. Therefore, if such tests are abn mal in a patient taking ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28, it is reco mended that they be repeated after the drug has been withdrawn for two months. 3. Under th influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata ma increase in size. 4. Because these agents may cause some degree of fluid retention, con tions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undia nosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with history of psychic depression should be carefully observed and the drug discontinued if th depression recurs to a serious degree. 7. Any possible influence of prolonge ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy on pituitary, ovarian, ad nal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance ha been observed in a significant percentage of patients on oral contraceptives. The mechanis of this decrease is obscure. For this reason, diabetic patients should be carefully observe while receiving ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy. 9. The ac of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVU 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 may mask the onset of the climacteric. 10. Th pathologist should be advised of ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐2 therapy when relevant specimens are submitted. 11. Susceptible women may experience a increase in blood pressure following administration of contraceptive steroids. 12. Cholestat jaundice has been reported in users of oral contraceptives. If this occurs, ORTHO-NOVU 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 should be discontinued. This condition is more likely t occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a h tory of cholestatic jaundice of pregnancy should be carefully observed durin ORTHO-NOVUM 1/50 ☐21 or ORTHO-NOVUM 1/50 ☐28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically s nificant association has been demonstrated between use of oral contraceptives and the f lowing serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebr thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has bee neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesion e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdomin bleeding.

The following adverse reactions are known to occur in patients receiving oral contrace tives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloatin breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after tre ment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, ras (allergic), mental depression, change in weight (increase or decrease), breast changes (te derness, enlargement and secretion), changes in cervical erosion and cervical secretion suppression of lactation when given immediately post-partum, rise in blood pressure in su ceptible individuals.

Although the following adverse reactions have been reported in users of oral contrace tives, an association has been neither confirmed nor refuted: anovulation post-treatme which tends to occur more frequently in women with a history of menstrual disorders, preme strual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headach intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginiti

The following laboratory results may be altered by the use of oral contraceptives: hepat function—increased sulfobromophthalein retention and other tests; coagulation tests increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase platelet aggregability; thyroid function—increase in PBI, and butanol-extractable prote bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determinatio

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OBSTETRICS

Intra-amniotic administration of 15(S)-15-methyl-prostaglandin $F_{2\alpha}$ for the induction of midtrimester abortion

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To determine the practicability of administering 15(S)-15-methyl-prostaglandin $F_{2\alpha}$-tromethamine (15(S)-15-Me-$PGF_{2\alpha}$) intra-amniotically for the induction of midtrimester abortion, initially 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ was administered to 20 physically healthy gravid women, and was repeated after 24 hours in those patients who had not aborted. Within 24 hours, 65 per cent aborted, and, within 36 hours, 95 per cent aborted. Although 67 per cent experienced emesis, no serious complications occurred. This abortion rate is similar to that obtained with the recommended dose schedule of the dosage of prostaglandin $F_{2\alpha}$ approved by the Food and Drug Administration and those reported with intra-amniotic administration of either hypertonic saline or urea when augmented with high, continuous, intravenous infusions of oxytocin. While the study intra-amniotic dose schedule appeared to be practicable, large, comparative studies will be necessary to determine the most satisfactory dose schedule and whether this method is more acceptable than other available methods.

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ACCEPTED METHODS of terminating midtrimester pregnancies in the United States include intra-amniotic administration of hypertonic saline (saline) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Intra-amniotic administration of $PGF_{2\alpha}$ appears to be more effective in that a higher proportion of patients abort within a shorter period of time, and it may eventually be demonstrated to be safer than hypertonic saline.[1] Side effects of emesis and diarrhea are more frequent with $PGF_{2\alpha}$, and a second dose of $PGF_{2\alpha}$ is required in about 30 per cent of patients.

Several analogues of $PGF_{2\alpha}$ have been tested. If these analogues are more uterine specific than the

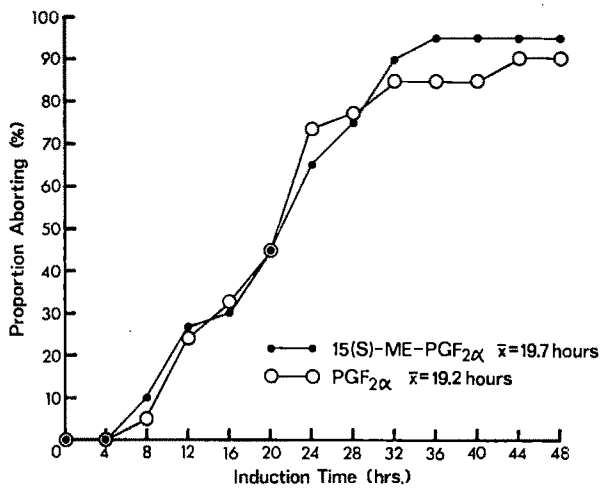


Fig. 1. Cumulative abortion rates (per cent) following intra-amniotically administered prostaglandin during the trial period in hours for: (1) 20 patients treated initially with 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ and repeated at 24 hours if abortion had not occurred, and (2) 22 patients treated initially with 40 mg. of $PGF_{2\alpha}$ and given 20 mg. at 24 hours if abortion had not occurred. $\overline{X}$ = Mean.

$PGF_{2\alpha}$, they may have fewer side effects; if they are more slowly metabolized to less active metabolites, single doses may be more effective. 15(S)-15-methyl-prostaglandin $F_{2\alpha}$ (15-Me-$PGF_{2\alpha}$) appears to be more potent and less rapidly metabolized than $PGF_{2\alpha}$.[2] This study was conducted to evaluate the practicability of administering intra-amniotic 15(S)-15-Me-$PGF_{2\alpha}$ for terminating midtrimester pregnancies.

Material and methods

Twenty physically healthy gravid women, from 18 to 33 years of age and 13 to 22 menstrual weeks' gestation who desired abortion, were aborted in the Clinical Research Unit of the University of North Carolina Memorial Hospital (Table I). All subjects received intra-amniotically 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ as the Tham salt in a concentration of 0.5 mg. per millimeter of diluent. This dose was repeated after 24 hours in those patients who failed to abort. Vital signs and oral temperature were obtained at hourly intervals until six hours after abortion was completed.

Twelve subjects had continuous monitoring of intra-amniotic pressure by the open-end catheter technique.[3] Monitoring was initiated 0.5 hour prior to the administration of 15(S)-15-Me-$PGF_{2\alpha}$ and continued until abortion of the fetus or until the trial was declared a failure. Only contractions of greater than 6 mm. of Hg in intensity were evaluated. Tonus was defined as the lowest pressure in millimeters of Hg

Table I. Characteristics of patients given intra-amniotic 15(S)-15-me-$PGF_{2\alpha}$

Age (yr.)	
Mean	21.8
Range	18-33
Parity, No. (%)	
Nulliparas	11(55)
Multiparas	9(45)
Gestational age (wk.)	
Mean	17.12
Range	13-22
<16 wk., No. (%)	8(40)
>16 wk., No. (%)	12(60)

Table II. Complications and side effects with intra-amniotic administration of 15(S)-15-Me-$PGF_{2\alpha}$ in 20 patients

	Patients	
Side effect	*No.*	*%*
Pain	18	90
Mean No. of doses of meperidine	3.35	
Range	0-13	
Fever(>100° F.)	4	20
Endometritis (suspected)	1	5
Emesis	13	65
Mean No. of episodes	1.9	
Range	0.7	
Antiemetics	7	35
Mean No. of doses	0.45	
Diarrhea	6	30
Mean No. of episodes	1.05	
Blood loss > 500 ml.	0	0
Incomplete abortion	8	40

above atmospheric pressure that occurred between contractions. Intensity was defined as the maximum pressure above tonus that occurred with each contraction. Uterine activity was calculated in Montevideo units (number of contractions in ten minutes times the mean intensity of contractions occurring within the ten-minute time period) and in Torr minutes. A Torr minute is equivalent to a pressure of 1 mm. Hg for a one-minute period of time[4] and is calculated by multiplying the intrauterine pressure in millimeters of Hg by the duration in minutes the pressure is maintained. A hand planometer was used to calculate area.

Peripheral venous blood specimens, obtained before prostaglandin administration, six hours after the initial dose, and after abortion, were analyzed for hematopoietic, hepatic, and renal parameters. Abortion was defined as "complete" when both the fetus and placenta were spontaneously expelled from the uterus, "incomplete" when the fetus was spontaneously ex-

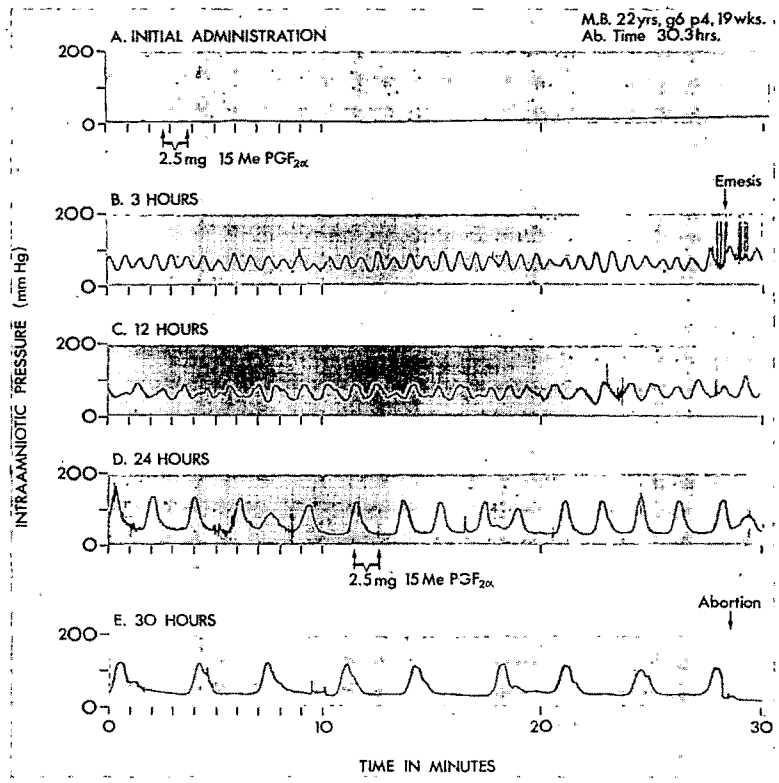


Fig. 2. Uterine activity at selected intervals in patient receiving intra-amniotic 15(S)-15-Me-$PGF_{2\alpha}$.

pelled from the uterus without complete expulsion of the placenta, and "failure" when neither the fetus nor the placenta was expelled from the uterus within 48 hours following the initial injection. Induction-to-abortion time was the time from initial prostaglandin administration to expulsion of the fetus. Subjects were observed up to six hours after abortion of the fetus for expulsion of the placenta. When analgesia was requested by the patient, 75 mg. of meperidine was administered intramuscularly. For persistent emesis, 10 mg. of prochlorperazine was administered intramuscularly at six-hour intervals.

Results

Following the initial administration of 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$, 13/20 patients (65 per cent) aborted within 24 hours, and 19/20 (95 per cent) aborted within 36 hours, with a mean induction-to-abortion time of 19.7 hours (Fig. 1). Eleven (55 per cent) aborted "completely," and eight (40 per cent) aborted "incompletely." One patient who received only 2.25 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ at 24 hours into the trial period, because of lack of available medication, was classified as a trial "failure."

Following intra-amniotic administration of 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$, there was a consistent evolution of uterine activity in individual subjects (Fig. 2) and shown by mean values (Fig. 3). After prostaglandin administration, tonus was increased within 20 minutes and frequent, low-intensity contractions were observed in all subjects within three hours. Uterine contractions evolved to become more intense and less frequent, with little change in tonus. Uterine activity as measured in Montevideo units and cumulative Torr minutes increased after $PGF_{2\alpha}$ administration and over the course of abortion (Fig. 3). Calculations are portrayed for only 90 per cent of the total abortion time since mechanical difficulties, including catheter obstruction, catheter prolapse, and rupture of membranes, frequently occurred just prior to the abortion and resulted in artifacts in the tracings.

Pain, emesis, diarrhea, and fever (>100° F.) were the most frequently occurring side effects or complications (Table II). Analgesia was requested by 18 subjects (90 per cent), and seven (35 per cent) were given an antiemetic. Three subjects (15 per cent) had fever (temperature > 100° F.) which occurred just prior to abortion and resolved spontaneously. One febrile patient was treated with antibiotics for suspected endometritis.

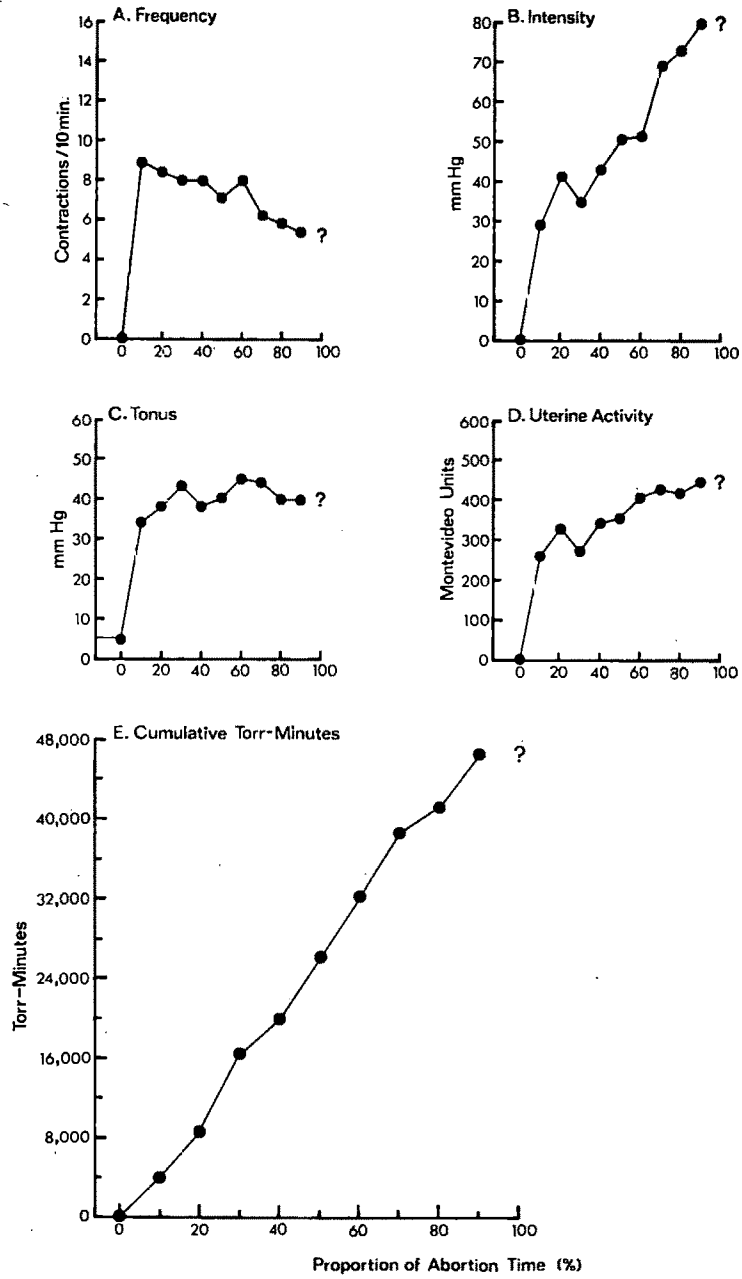


Fig. 3. Uterine contractility studies in 12 patients monitored after receiving intra-amniotic 15(S)-15-Me-$PGF_{2\alpha}$.

One subject, after receiving a 0.5 mg. test dose of 15(S)-15-Me-$PGF_{2\alpha}$ without side effects, exhibited intense pelvic pain, emesis, cough, and ruptured membranes immediately after receiving an additional 2.0 mg. Symptoms resolved spontaneously after one hour and 40 minutes. Another patient, following a clear transabdominal amniocentesis and insertion of an intra-amniotic catheter, but prior to prostaglandin administration, experienced emesis, shortness of breath without clinical evidence of bronchospasm, and mottled discoloration over the face and anterior chest. After all symptoms had resolved spontaneously within four minutes after onset, the intra-amniotic catheter was withdrawn slightly; clear amniotic fluid was again aspirated, and a 2.5 mg. dose of 15(S)-15-Me-$PGF_{2\alpha}$ was administered without ill effects. One subject, 2.5 hours after induction of abortion and 0.5 hours after administration of 75 mg. of meperidine intramuscu-

larly, developed an irregular pulse with a heart rate of 64 beats per minute and blood pressure of 94/50 mm. Hg. Although she was asymptomatic, an electrocardiogram revealed a 2° heart block. Mobitz type I (Fig. 4). She responded within one hour to intravenous atropine with the resumption of a regular pulse, accompanied by an increase in heart rate and blood pressure to normal limits, and manifested no further cardiovascular symptoms.

No clinically or statistically significant changes occurred in mean hematocrit, platelet count, serum creatinine, blood urea nitrogen, electrolytes, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, or bilirubin over the course of drug administration. The mean white blood cell count increased from a preinduction value of 9,174 to 14,955 per cubic millimeter (statistically significant, $P < 0.01$) after abortion, while the proportion of neutrophils increased (but not significantly) from 67 to 73 per cent over this period of time.

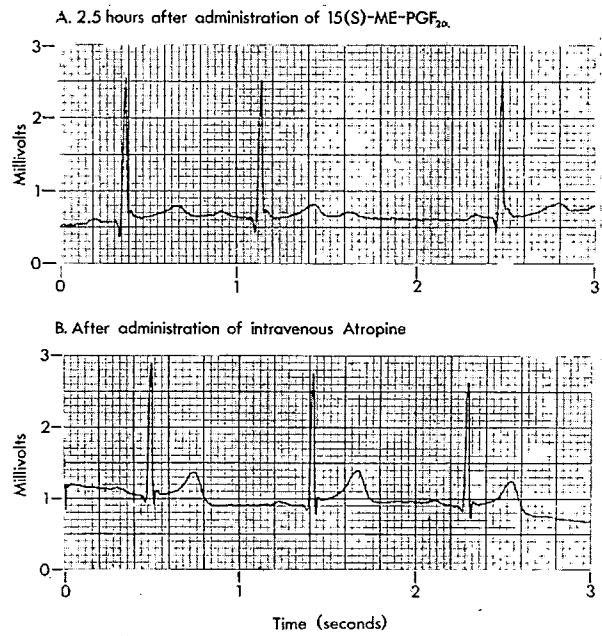


Fig. 4. Electrocardiogram in patient with 2° heart block, Moritz type I, before and after atropine therapy.

Comment

Following the report of animal studies which demonstrated that the analogue, 15(S)-15-Me-$PGF_{2\alpha}$, is both more potent and longer acting than the parent compound, $PGF_{2\alpha}$,[2] preliminary studies were undertaken to evaluate the effect of 15(S)-15-Me-$PGF_{2\alpha}$ on uterine contractility in human subjects.[5]

The intra-amniotic administration of 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ appears to be practicable for inducing midtrimester abortion, in that high abortion rates occurred within a short period of time, with clinically acceptable side effects. The rates of abortion occurring in this pilot study are similar to those reported by Wiqvist and associates[5] with 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$ injected intra-amniotically, and Karim and Sivasamboo using either 1.0 or 2.5 mg.[6]

Similar rates of abortion have been obtained with other agents (intra-amniotic $PGF_{2\alpha}$, intra-amniotic hypertonic saline, and urea augmented with intravenous oxytocin). Intra-amniotic administration of 40 mg. of $PGF_{2\alpha}$, followed by 20 mg. at 24 hours if abortion had not occurred, resulted in 91 per cent abortions within 48 hours (mean = 19.2 hours).[7] A nearly identical cumulative abortion rate was found in the present study with 2.5 mg. of 15(S)-15-Me-$PGF_{2\alpha}$; 65 per cent aborted in 24 hours, and 95 per cent had aborted by 36 hours, in a mean time of 19.7 hours (Fig. 1). Rates of vomiting, diarrhea, pain, fever, and the evolution of uterine activity were similar.[7]

Administration of saline or urea, even with continuous intravenous oxytocin augmentation, appears less effective than the present study method. Among 3,943 subjects who had abortion induced with intra-amniotic instillation of 200 ml. of 20 per cent saline and augmented with continuous intravenous oxytocin, 45 per cent aborted within 24 hours and 90 per cent aborted within 48 hours (mean = 35.2 hours).[8] With the intra-amniotic administration of 80 Gm. of urea and continuous intravenous oxytocin augmentation at rates greater than 100 ml. per minute, 67 per cent aborted within 24 hours and 87 per cent aborted within 48 hours (mean = 26.4 hours).[9]

Cardiac arrythmias have been reported with the use of $PGF_{2\alpha}$. The occurrence of a 2° heart block in one of our patients is the first reported in association with 15(S)-15-Me-$PGF_{2\alpha}$ and may have been related to administration of meperidine or secondary to pain. Its disappearance after atropine administration is a typical response of this phenomenon which results from a variety of causes. Hence, any causal relationship to the prostaglandin analogue use remains speculative.

Intra-amniotic administration of multiple doses of 15(S)-15-Me-$PGF_{2\alpha}$ is practicable for the induction of midtrimester abortion but does not appear to have significant advantages over $PGF_{2\alpha}$. Although the analogue is more potent and longer acting, it does not appear to be more specific in its abortifacient action. Further studies will be necessary to determine whether single-dose schedules of this analogue will be more satisfactory than single intra-amniotic dose schedules of $PGF_{2\alpha}$.

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Satisfaction with medical care during pregnancy and delivery

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Societal attitudes toward the medical profession are apparently undergoing a change from awe and total respect to a more critical assessing of accountability and credibility. Based on mass media reports and the increasing number of malpractice suits, it would appear that a rational, unbiased review of medical doctors, hospital personnel, and care received is in order. This review should be concerned with technical aspects of medicine as determined by highly competent professionals and the consumer's view of the medical care he receives. The latter review should logically be taken directly to the consumers of medical care to determine their satisfaction with the care they received. Because of the varied areas of specialty within the medical profession, there are different types of relationships between doctors and their patients. The obstetrician, for instance, is usually associated with pregnancy as a joyful event, in contrast to a surgeon whose diagnosis may seldom be accompanied by joy. Satisfaction with medical care could thus be expected to vary according to the area of specialty and may be related to factors over which doctors have no control, factors which initially bring the patient to the doctor for care. The degree of anxiety related to the patient's condition could also be expected to contribute to the degree of satisfaction expressed by the patient.

IT HAS BEEN WELL established that all women experience an increase in anxiety during pregnancy.[1-5] Because patient needs are psychological, as well as physiologic, the pregnant woman's doctor is indeed a crucial person in her life, as is the hospital staff during confinement. They are in a supreme position to influence psychological functioning and concomitant physiologic response. In fact, the degree to which all needs are met can be expected to influence the outcome of the patient's hospital confinement and, accordingly, her degree of satisfaction with her medical care.

Recent research concerning maternity patients indicates they are concerned about the social and psychological aspects of medical care, specifically staff attitudes and routine ward procedures.[6, 7] A 1972 survey of hospital patients indicated that despite a high level of satisfaction 17 per cent of the patients would choose not to return to the same hospital for care.[8] The primary reason given related to the hospital's not meeting the patient's expectations. In recent years, some women throughout the United States have begun establishing their own separate health-care centers that specialize in obstetric-gynecologic care and reproductive information. These centers offer classes, counseling, and instruction in "self-help" techniques. A current publication lists 44 such centers.[9] While the precise reasons for this movement to establish separate and specific facilities for female health care are not known, it may indicate a degree of dissatisfaction with present health-care systems.

It was with the foregoing views in mind that this study was planned, the purpose of which was to determine satisfaction of maternity patients with medi-

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Table I. Characterization of the sample

Characteristic	*Category*	*Respondents in each category*	
		*Number**	*Per cent*
Number of pregnancies	Primiparas	133	46.9
	Multiparas	150	53.1
Total		283	100.0
Age	Under 20	34	12.1
	20-35	238	84.4
	Over 36	10	3.5
Total		282	100.0
Husband's occupation	Professional	116	46.1
	Nonprofessional	95	37.7
	Farm	19	7.5
	Student	22	8.7
Total		252	100.0
Women's occupation	Professional	53	19.3
	Nonprofessional	68	24.7
	Housewife and/or mother	147	53.5
	Student	7	2.5
Total		275	100.0
Woman's educational level	High school or less	129	46.3
	Trade school or some college	112	40.1
	Bachelor's degree or beyond	38	13.6
Total		279	100.0
Family's yearly income	Public assistance	21	7.8
	Under $5,000	23	8.5
	$ 6,000-$10,000	83	30.7
	$11,000-$15,000	91	33.7
	$16,000-$19,000	31	11.5
	$20,000 And over	21	7.8
Total		270	100.0

*Number = 291; however, each category does not equal this number because not all subjects answered every question.

cal care they received during pregnancy and delivery and the relationship between the degree of expressed satisfaction and the number of pregnancies or the educational level of the woman.

Methods and material

The term "satisfaction," as used in this paper, is defined as a generalized positive attitude toward a situation and persons involved in that situation. Four categories of medical care were chosen for investigation: doctor care during pregnancy, doctor care during labor and delivery, hospital care during labor, and hospital care during and following delivery. Areas studied within those categories were specific medical procedures, personal relationships with medical staff, and affective and instrumental communication.

The research instrument, with a Likert-type rating scale and open-ended questions used to assess satisfaction, was administered to 291 maternity patients during their confinement following childbirth in five midwestern hospitals (Table I). Subjects were not matched in terms of any factor except having recently given birth, but grouping according to number of pregnancies and educational level was done in the statistical analysis. Subjects delivered by cesarean section were omitted.

Data were analyzed with the use of frequency counts and percentages. The chi-square test was used to determine statistical differences.

Results

The results of this study indicate that 88.8 per cent of the subjects were satisfied with their doctor's professional competence (Table II). Eighty-two per cent reported feeling that they could trust their doctor's judgment in matters dealing with pregnancy and delivery. Slightly fewer, 81.5 per cent, felt comfortable with the doctor. Eighty per cent of the subjects were satisfied that they could ask their doctor questions related to pregnancy and delivery, but only 68.8 per cent reported believing that their doctor understood their feelings. There were no statistically significant differences between subjects of varied educational levels or between primiparas and multiparas.

Less than three fourths of the subjects expressed satisfaction with any aspect of doctor care during the

Table II. Satisfaction with doctor care during pregnancy

Satisfaction with doctor care during pregnancy	*Subjects expressing satisfaction (per cent)*
1. Satisfied with doctor's professional competence	88.8
2. Satisfied I could turst the doctor's judgment about my pregnancy	82.6
3. Satisfied with feeling comfortable with the doctor	81.5
4. Satisfied that I could ask the doctor questions	80.5
5. Satisfied that the doctor understood my feelings	68.8

Table III. Satisfaction with doctor care during labor and delivery

Aspect of care	*Subjects expressing satisfaction (per cent)*
1. Satisfied the doctor treated my emotional and physical state	72.6
2. Satisfied the doctor understood my feelings	69.9
3. Satisfied with amount of time doctor was with me	67.8
4. Satisfied that the doctor explained procedures	62.2
5. Satisfied that the doctor explained medications	58.3

labor process (Table III). Satisfaction that the doctor treated their emotional and physical states was expressed by 72.6 per cent. Almost 70 per cent of the subjects were satisfied that the doctor understood their feelings while 67.8 per cent indicated satisfaction with the amount of time the doctor was with them. The doctor's explanation of procedures was satisfactory to 62.2 per cent of the subjects while 58.3 per cent were satisfied that the doctor explained medications. Women of higher-education levels expressed less satisfaction with the doctor's explanation of medication than did women of lower educational levels ($P < 0.01$; Chi square = 12.39; degrees of freedom = 4). There were no statistically significant differences between primiparous and multiparous women in expressed satisfaction with doctor care during labor.

Ninety-two per cent of the subjects in this study indicated they were satisfied with the amount of individualized attention they received from the hospital staff (Table IV). Eighty-five per cent were satisfied that the hospital respected their wishes and explained

Table IV. Satisfaction with hospital care during labor and delivery

Aspect of care	*Subjects expressing satisfaction (per cent)*
1. Satisfied with amount of individualized care	92.2
2. Satisfied that hospital respected my wishes	85.3
3. Satisfied that staff explained procedures	85.1
4. Satisfied that the staff understood my feelings	84.5
5. Satisfied with medication during labor	71.1

Table V. Satisfaction with hospital care during and following delivery

Aspect of care	*Subjects espressing satisfaction (per cent)*
1. Satisfied with emotional support received while in the hospital following delivery	89.9
2. Satisfied with amount of individualized care received	86.0
3. Satisfied with baby-care information offered by hospital	84.6
4. Satisfied with hospital medications	79.7
5. Satisfied with episiotomy	78.2
6. Satisfied with being strapped down during delivery	72.2
7. Satisfied with contraceptive information I received in the hospital	60.0

procedures. Slightly fewer, 84.5 per cent, were satisfied that the staff understood their feelings.

Satisfaction with emotional support received while in the hospital following delivery was expressed by 89.9 per cent of the subjects (Table V). Eighty-six per cent indicated they were satisfied with the amount of individualized care received, and 84.6 per cent indicated satisfaction with baby-care information offered by the hospital. Satisfaction with hospital medications was expressed by 79.7 per cent of the population. Slightly over 78 per cent indicated satisfaction with episiotomy, while 72.2 per cent were satisfied with being strapped down during delivery. Sixty per cent of the subjects were satisfied with the contraceptive information they received while in the hospital. There were no statistically significant differences between

multiparous and primiparous women, or between subjects of varied educational levels, in their expressed satisfaction with hospital obstetric care.

Seventy-one per cent were satisfied with the medication they received during labor. There were no statistically significant differences between women of varied educational levels in their expressed satisfaction with hospital care during labor.

Comment

Comparison of the percentages of subjects expressing satisfaction in each of the four categories—doctor care during pregnancy, doctor care during labor, hospital care during labor, and hospital care during and following delivery—indicates that the greatest percentage of women (92.2) expressed satisfaction with the amount of individualized attention they received from the hospital staff during labor. Satisfaction with the doctor's explanation of medications used during labor and delivery received the lowest (58.3) percentage of positive responses in this study. Sixty-two per cent of the subjects were satisfied that the doctor explained procedures during labor and delivery.

It is difficult to explain the relatively low percentage of satisfaction in the areas of doctor's explanations to their patients without knowledge of the actual explanations that took place. Perhaps the doctors did not give a satisfactory explanation of medication used. It may be very difficult for doctors to explain the complex technicalities of procedures and medications in terms the lay person can understand. On the other hand, perhaps doctors are underestimating their patient's ability to understand something that so directly affects them. However, it is possible that with the trend toward lighter medication during childbirth women also receive less relief from pain. Is it possible that subconscious factors were operating here? Perhaps, in fact, it was not the doctor's explanation that was lacing but rather less relief from pain than the subjects thought they could expect. If indeed this is an area where there is a lack of communication between doctor and patient, it might be an area where childbirth education in these specific areas before the traumatic time of childbirth would prove beneficial.

Satisfaction with doctor care during pregnancy was generally higher than was satisfaction with doctor care during labor and delivery. Several factors may account for this. The very nature of the labor and delivery process, i.e., extremely critical and demanding of the doctor, may not allow the doctor to devote time to the psychological needs of the woman, and it does not always allow the doctor to verbalize extensively as he devotes his attention to the crucial birth process. The amount of time the doctor spends with his patient during labor is usually not entirely under his control. They must frequently leave office calls to attend to deliveries and rush back to see the waiting patient. The labor and delivery process is much different from the pregnancy period. Generally, it can be assumed that the woman is not as physically uncomfortable during pregnancy as she is during delivery. She may associate satisfaction with the doctor during delivery with his ability to relieve physical discomfort, which he is, to a large degree, unable to do.

Comparison of the two categories concerned with hospital care versus the two categories concerned with doctor care indicates generally higher percentages of satisfaction as a whole for hospital care. Eighty-five per cent of the subjects were satisfied that the hospital staff explained procedures used during labor compared with 62 per cent who were satisfied that the doctor explained procedures used during labor and delivery. Almost 85 per cent of the subjects were satisfied that the hospital staff understood their feelings during labor and delivery while only 69.9 per cent were satisfied that the doctor understood their feelings. This difference could be due to several factors. The responsibility of a safe delivery actually rests with the doctor. Perhaps this demands his attention more than do the women's emotional needs. Or could it be a "sexist factor"? Generally, the hospital staff is female while the doctor is usually male. Do women have greater empathy for another woman in childbirth than does a man? Is it, in fact, easier for a woman to relate to another woman in this aspect of life peculiar only to them? Perhaps this could account for the generally over-all higher percentage of expressed satisfaction with hospital care than with doctor care.

Satisfaction with contraceptive information was expressed by only 60.3 per cent of the subjects in this study. The type of information the subjects received is not known; however, it would seem logical that hospitals should first ascertain the type of information the patient desires. It may be that the patient is not satisfied with contraceptives rather than with the information she receives about contraceptives.

Apparently satisfaction, as expressed by the subjects in this study, with medical care was not generally influenced by educational level or state of parity. The chi-square test was used to determine levels of significance. Only one aspect of care, the doctor's explanation of medication, was significantly different for women of varied educational levels. Based on the results of this study, the assumption can be made that women, regardless of state of parity or educational level, perceive factors satisfying their needs to be quite

homogeneous. Indeed, perhaps the psychological needs of women basically do remain the same for all women during childbirth. Likewise, viewing the doctor as competent and trustworthy does not appear to be influenced by the women's educational level or state of parity.

Conclusion

Based on the results of this study, there appears to be a communication gap between doctor and patient in the field of obstetrics. While 88.8 per cent were satisfied with their doctor's competence, only 68.8 per cent were satisfied that their doctor understood their feelings during pregnancy. Likewise, the doctor's explanations of procedures and medications were viewed as satisfactory by 62.2 and 58.3 per cent, respectively, of the subjects. Two suggestions are offered to improve this situation: (1) an increased emphasis in medical training programs on doctor-patient relationships, (2) a public education attempt to bring patients' expectations of the physician to be more realistically attuned to what the doctor is able to do in view of limitations placed upon him by his heavy patient load.

Critics of hospital care should be cognizant of the high percentages of maternity patient satisfaction expressed toward hospital care in this study. It is indeed noteworthy that 92.2 per cent of the subjects in this study were satisfied with the amount of individualized attention they received during confinement.

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Circulating maternal serum progesterone in high-risk pregnancies

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Serum progesterone was measured by competitive protein-binding assay in 331 cases of normal pregnancy ranging from 6 to 42 weeks. Serial estimations of serum progesterone were performed in nine cases of severe hypertensive disorder of pregnancy, eight cases of twin pregnancy, three cases of twin pregnancy complicated by severe hypertensive disorder of pregnancy, three cases of triplet pregnancy, three cases of previous bad obstetric history, one case of anencephaly, and seven cases of intrauterine fetal death. Serum progesterone remained within normal range in severe hypertensive disorder of pregnancy and the levels were indistinguishable in cases of fetal growth retardation from those without growth retardation. In twin and triplet pregnancies, serum progesterone was within normal range or elevated and was usually higher than normal in twin pregnancies after weeks 33 to 34. Serum progesterone levels were normal in anencephalic pregnancy and in most cases of intrauterine fetal death. The findings are discussed with reference to placental hormonal activity. It is concluded that serum progesterone is a poor index of placental function.

UNTIL RECENTLY, urinary pregnanediol has been suggested as a placental function test.[1–4] It is based on the premise that since urinary pregnanediol is the urinary metabolite of progesterone which is synthesized mainly by the placenta without need of fetal participation, it would reflect placental secretory function satisfactorily. Urinary pregnanediol excretion in pre-eclampsia has been reported to be below the normal range[5–7] but its practical usefulness as a placental function test is limited by the wide scatter and considerable overlap with values found in normal pregnancy,[4–8] as well as its lack of absolute reliability in predicting impending fetal death.[9] Aubry and Nesbitt[10] found urinary pregnanediol less striking in usefulness than urinary estriol in chronic hypertension in pregnancy, and no correlation with fetal prognosis could be found by other workers.[11, 12] The large coefficient of variation of urinary pregnanediol of up to 24 per cent in normal pregnancy[13] and the much larger variation (32 per cent) in severe toxemia[8] render interpretation of urinary pregnanediol in toxemia difficult and unreliable. However, in pregnancies with fetal growth retardation, urinary pregnanediol excretion was low[1–4, 14, 15] and correlated well with fetal and placental weights in pre-eclamptic toxemia.[1, 4, 14]

Since urinary pregnanediol is the urinary metabolite of progesterone which is produced by the placenta in pregnancy and without fetal participation, serum progesterone like serum human chorionic somatomammotropin (hCS) (produced solely by the placenta without fetal participation) might serve as an index of placental function. Using fluorimetry, Short and Eton[16] found plasma progesterone levels in pre-eclampsia within the normal range. Kalpana and associates[17] found a drop in the mean serum progesterone in 12 cases of toxemia of pregnancy at weeks 34 to 36 of pregnancy but a subsequent rise at 37 to 39 weeks. In 11 patients with severe pre-eclampsia and subsequent intrauterine deaths, Tulchinsky and Okada[18] found that plasma progesterone was unable to predict impending fetal death and remained unchanged in most cases even after intrauterine death had occurred.

Using fluorimetry and gas liquid chromatography, respectively, Short[19] and Yannone and associates[20] found high levels of plasma progesterone in twin

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pregnancy compared to single normal pregnancy. However, Greig and associates[21] found plasma progesterone in twin pregnancy to be not different from those found in single normal pregnancy and attributed the level of progesterone to be dependent on the size of the fetus and thus to some extent on the amount of functional placental tissue.

With the availability of a rapid competitive protein-binding assay or radioimmunoassay of plasma or serum progesterone, this could prove to be a rapid method of evaluating placental function. This study was carried out to determine (1) the levels of maternal serum progesterone in twin and triplet pregnancies (complicated and uncomplicated), in pregnancies with severe pre-eclampsia or bad obstetric histories, and in pregnancies with intrauterine fetal deaths, and (2) if circulating maternal serum progesterone is a good index of placental or trophoblastic function.

Materials and methods

Subjects. The study was carried out in 11 cases of twin pregnancy, three cases of triplet pregnancy, nine cases of severe hypertensive disorder of pregnancy, three cases of bad previous obstetric history, seven cases of intrauterine fetal death, and one case of anencephaly. Severe hypertensive disorder of pregnancy was diagnosed when the diastolic blood pressure was 110 mm. Hg or more or when the diastolic blood pressure was 100 mm. Hg or more together with albuminuria. Serial peripheral venous blood samples were collected from the patients between 09:00 and 12:00 hours by venipuncture into a plain Vacutainer. The sera were separated off within 2 hours of collecting the blood and stored at −20° C. until assayed. In the seven cases of intrauterine deaths, only a single blood sample was obtained as the patients were either unbooked, wanted induction for fetal death, or were in labor with an intrauterine dead fetus when they first appeared. Three of the 11 cases of twin pregnancy developed hypertensive disorder of pregnancy and one patient had a conjoined twin with two heads and necks but a single trunk, two pairs of limbs, and a pair of adrenal glands.

To determine the serum progesterone levels in normal pregnancy, 331 samples of peripheral venous blood obtained from patients with single normal pregnancy, who had regular monthly cycles and who were certain of their last menstrual period, were assayed. In the cases of induced abortion the products of conception were examined histologically and confirmed to be normal pregnancy and in the other cases the babies delivered were checked and found to be healthy babies.

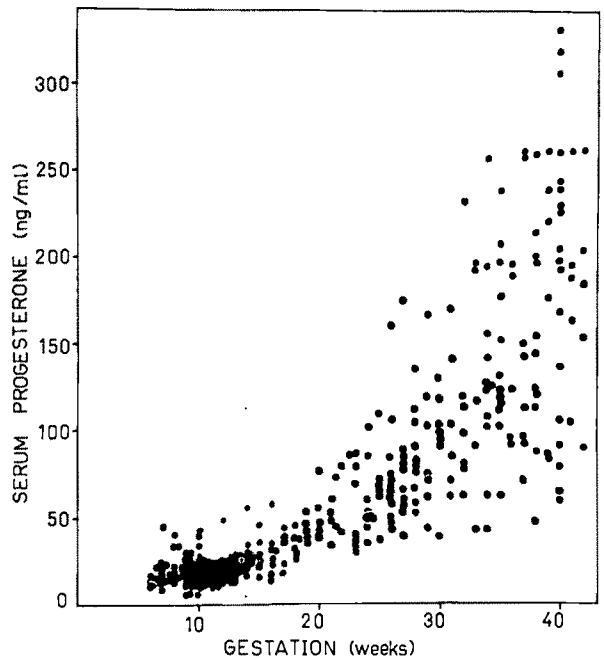


Fig. 1. Scattergram of serum progesterone throughout normal pregnancy. As many of the serum progesterone levels in early pregnancy were very close in values, an appearance of fusion of the dots at this stage of pregnancy is obtained.

Progesterone assay. Serum progesterone was assayed by the rapid competitive protein-binding assay of Johansson[22] with minor modification.[23] A 100 μl sample of serum was extracted with petroleum ether (boiling point 30° to 40° C., BDH Lot No. 1598330) which gave selective extraction of progesterone. Recovery and procedural losses were monitored by the addition of progesterone 1, 2-H3 (n) (specific activity = 169 mCi per milligram, Amersham, England) prior to extraction. The binding protein used was plasma obtained from women on the combined oral contraceptive pill. Precision, accuracy, and reliability were within acceptable limits. In the cases of abnormal pregnancies described above, whenever the progesterone level obtained was extremely low or excessively high, serum progesterone of the same sample was reassayed by both the competitive protein-binding (CPB) method and radioimmunoassay (RIA) with an antiserum raised against progesterone-11-oxime bovine serum albumin conjugate, as described by Morgan and Cooke.[24] The petroleum ether extract of the serum was chromatographed on Sephadex LH-20 column with chloroform-heptane-ethanol (200:200:1, v/v/v) as described before.[23] The difference between the results obtained by RIA and CPB on the same sample was usually 10 per cent or less.

Table I. Maternal serum progesterone during normal pregnancy (n = 331)

Gestation (wk.)	*No. of samples*	*Range of serum progesterone (ng./ml.)*	*Mean serum progesterone ± S.E. (ng./ml.)*	*S. D.*
6	5	13.2- 17.1	15.0 ± 0.8	1.8
7	10	9.9- 45.8	21.0 ± 3.2	10.2
8	10	13.2- 40.8	22.8 ± 3.2	10.1
9	20	7.9- 30.2	18.8 ± 1.4	6.4
10	23	7.9- 43.4	19.9 ± 1.8	8.9
11	20	14.5- 23.5	19.7 ± 0.8	3.5
12	10	18.3- 49.2	24.5 ± 3.1	9.8
13	10	17.1- 30.8	25.5 ± 1.9	5.9
14	10	17.4- 56.8	29.6 ± 3.5	10.9
15	6	17.2- 45.1	29.6 ± 4.0	10.0
16	8	17.8- 59.0	31.4 ± 4.6	13.2
17	5	19.1- 45.0	33.6 ± 5.0	11.3
18	6	29.6- 46.0	39.2 ± 2.6	6.3
19	5	38.4- 53.9	44.4 ± 2.9	6.4
20	5	39.6- 77.6	52.8 ± 6.8	15.2
21-22	8	34.4- 80.2	55.5 ± 5.6	15.8
23	8	21.0- 87.8	59.0 ± 8.7	24.6
24	8	36.8-103.9	60.8 ± 8.0	22.7
25	7	38.2-111.8	68.2 ± 8.6	22.7
26	12	46.1-164.5	75.6 ± 9.5	32.8
27	10	40.2-178.9	80.5 ± 11.9	37.8
28	10	52.6-112.0	86.8 ± 8.1	25.5
29	7	44.4-168.4	92.5 ± 15.8	41.9
30	7	39.5-131.6	97.9 ± 11.1	29.2
31	6	63.2-171.1	106.7 ± 17.4	42.6
32	7	64.5-235.5	113.9 ± 21.5	56.9
33	5	42.1-198.7	129.7 ± 30.6	68.5
34	11	44.7-259.2	132.6 ± 17.8	59.1
35	13	20.4-240.8	135.8 ± 16.3	58.8
36	5	94.7-198.8	141.1 ± 22.6	50.6
37	9	72.4-263.2	148.7 ± 23.3	69.9
38	11	48.2-263.2	153.2 ± 18.8	62.4
39	6	88.2-263.2	180.2 ± 31.0	75.9
40	18	60.5-263.2	192.9 ± 20.5	87.2
41	5	106.6-263.2	184.5 ± 25.4	56.8
42	5	90.8-263.2	179.9 ± 28.4	63.5

Table II. Relevant clinical details of patients with severe hypertensive disorder of pregnancy in whom serum progesterone was determined

Case No.	*Patient*	*Age*	*Parity*	*Highest blood pressure*	*Urine albumin*	*Clinical features*	*Gestation at delivery (wk.)*	*Birth wt. (Gm.)*	*Apgar score*	*Placental wt. (Gm.)*	*Serum p. prior to delivery (ng./ml.)*
1	S. K. H.	24	1	150/105	++	Severe PET* from 28 wk.; spontaneous labor at 33wk; normal delivery	33.2	2,013	8 alive	340	113
2	C. M. L.	32	0 + 3	130/100	+	PET from 32 wk.; spontaneous labor; LSCS* for contracted pelvis	35	2,840	8 alive	454	118
3	S. B. T.	35	6	150/110	Nil	Threatened abortion at 14 wk.; severe PET from 31 wk.; normal delivery at 36 wk.	36	2,555	10 alive	397	158

Table II—Cont'd

Case No.	*Patient*	*Age*	*Parity*	*Highest blood pressure*	*Urine albumin*	*Clinical features*	*Gestation at delivery (wk.)*	*Birth wt. (Gm.)*	*Apgar score*	*Placental wt. (Gm.)*	*Serum p. prior to delivery (ng./ml.)*
4	E. K. C.	21	0	150/110	+	Severe PET from 31 wk.; induced at 36.5 wk.; meconium present LSCS	36.5	1,788 (dysmature)	7 alive	NA*	118
5	C. A. M.	36	3	180/100	Trace	Two previous LSCS; essential hypertension; rt. eye blind, on debrisoquine sulfate for 3 yr.; renal function normal; induced; normal delivery	38	2,760	10 alive	454	228
6	W. L. T.	41	3	160/100	Trace	PET from 28 wk.; induced at 40 wk.; normal delivery	40	2,715	10 alive	454	144
7	Y. S. H.	38	1	180/110	++	Severe PET from 31 wk.; from 35 wk., uterus remained smaller than dates; induced at 37.5 wk.	37.5	1,305 (dysmature)	5 alive	NA	118
8	T. D.	22	0	140/100	Trace	Previous LSCS for PET; at 37 wk. PET; induced at 41 wk.; LSCS for failed induction	41	2,637	5 alive	NA	328
9	C. S. W.	39	0	150/110	Trace	Elderly primigravida with PET from 28 wk. LSCS for elderly primigravida and severe PET	38.5	2,690	10 alive	454	116

*PET = pre-eclamptic toxemia; LSCS = lower segment cesarean section; NA = not available.

Results

1. Normal pregnancy. Table I gives the mean ± standard error of the mean (S.E.) and the standard deviation (S.D.) of serum progesterone obtained in 331 cases of normal pregnancy in Asian women and Fig. 1 shows the scattergram of serum progesterone throughout gestation in normal pregnancy. There is a steady rise in serum progesterone throughout pregnancy and a more rapid rise after week 30 of gestation.

2. Hypertensive disorder of pregnancy. The pattern of serial serum progesterone levels in nine patients with severe hypertensive disorder of pregnancy is shown in Fig. 2 and the relevant clinical details and fetal outcome are shown in Table II. Two patients (Nos. 4 and 7, Table II) delivered small-for-dates infants when compared to the birth weights of babies in Singapore women.[25] There was no consistent trend in the pattern of serial serum progesterone in patients with hypertensive disorder of pregnancy which could be correlated with clinical severity and outcome of the pregnancy. Most of the values, including those of No. 4 (Table II), were within the one standard deviation range of the mean serum progesterone in normal pregnancy. There was wide fluctuation in the serial serum progesterone in the same patient. In one small-for-dates infant (No. 7, Table II) the serum progesterone was 45 ng. per milliliter at 35 weeks but increased quickly thereafter to 118 ng. per milliliter at 37.5 weeks.

Table III. Relevant clinical details of three patients with twin pregnancy and associated hypertensive disorder of pregnancy

Case No.	*Patient*	*Age*	*Parity*	*Highest blood pressure*	*Urine albumin*	*Clinical features*
1	T. E. N.	30	0	160/110	Nil	PET* at 30 wk.; twins with hydramnios, PET poorly controlled; induced at 35.5 wk.; Breech and forceps delivery
2	M. S.	29	0	130/90	+	PET at 34 wk.; Threatened abortion in early pregnancy; induced at 39 wk; LSCS for fetal distress
3	A. C.	33	0	160/120	+	PET from 36 wk.; spontaneous labor at 38 wk.; delivered by venthouse

*PET = Pre-eclamptic toxemia.

Table IV. Relevant clinical details of three patients with previous bad obstetric history

Case No.	*Patient*	*Age*	*Parity*	*Highest blood pressure*	*Urine albumin*	*Clinical features*	*Gestation at delivery (wk.)*	*Birth wt. (Gm.)*	*Apgar score*	*Placental wt. (Gm.)*	*Serum p. prior to delivery (ng./ml.)*
1	M. S.	33	3*	160/100	+	3 previous stillbirths; uneventful antepartum until 33.5 wk. when blood pressure rose to 160/100 and had abruptio placentae; LSCS; baby developed transient respiratory distress syndrome	33.5	1,701 (premature)	8	369	189
2	G. D.	30	1 + 1	120/180	Nil	Previous abortion and premature labor; asthmatic on bronchodilators; no PET; rest from 32 wk.; clinical signs of intrauterine growth retardation; Elective LSCS done at 38.5 wk.	38.5	1,873 (dysmature)	4 died	340	121
3	C. W. Y.	17	3	120/70	Nil	Three hydrops fetalis due to α-thalassemia; patient and husband α-thalassemia carriers; has mitral incompetence (rheumatic heart disease); induced at 42 wk.; normal delivery	42	3,125	10 alive	454	230

3. Twin and triplet pregnancy. The serial serum progesterone pattern in 11 cases of twin pregnancy and three cases of triplet is shown in Figs. 3 and 4, respectively, and the relevant clinical details of three cases of twin pregnancy with hypertensive disorder of pregnancy are given in Table III. The distribution of values of serum progesterone in twin pregnancy appears to cluster around two areas. Before weeks 33 to 34 of gestation, serum progesterone values in twin pregnancy were mainly within the standard deviation range for normal pregnancy, but after the weeks 33 to 34 the maternal serum progesterone levels were mainly above the standard deviation range and in at least five instances were above 300 ng. per milliliter. Serum progesterone concentrations in three cases of twin pregnancy with hypertensive disorder of pregnancy remained high or within the standard deviation for normal pregnancy and did not show any appre-

Gestation at delivery (wk.)	*Birth wt. (Gm.)*	*Apgar score*	*Placental wt. (Gm.)*	*Serum p. prior to delivery (ng./ml.)*
35.5	1,702(M)	10	680	283
	2,582(M)	10		
		both alive		
39	3,110(M)	8	NA	250
	2,685(M)	8		
		both alive		
38	2,010(M)	10	850	200
	2,637(M)	10		
		both alive		

ciable drop. In one patient who had a conjoined twin that was a double-headed monster with a single trunk, two pairs of limbs, and a pair of adrenal glands, serum progesterone remained within normal range and fell slightly after term (Fig. 3). There is a trend or suggestion that serum progesterone levels decline in twin pregnancy from week 38 or 39 onward.

With the three cases of triplet pregnancy, serum progesterone were slightly elevated and on the upper side of the standard deviation range for normal pregnancy. One patient with triplet pregnancy produced a conjoined twin which was a thoracoabdominopagus, had two pairs of adrenal glands, and has been described in detail elsewhere.[25] This patient had normal values of serum progesterone.

4. Intrauterine deaths. In five out of seven cases of intrauterine fetal death, serum progesterone levels were below the standard deviation range for the corresponding gestational age in normal pregnancy (Fig. 5). The remaining two cases had serum progesterone concentrations within the standard deviation range for normal pregnancy. The maternal serum progesterone ranged from as low as 19 to as high as 120 ng. per milliliter. All seven patients gave birth to macerated still births.

5. Bad obstetric history. Table IV shows the relevant clinical details of the three patients with poor previous obstetric performance who were studied. All three patients had serial serum progesterone within the standard deviation range for normal pregnancy (Fig. 5). In one patient who had delivered a growth-retarded baby (Case 2, Table IV) who died in the neonatal period, the last maternal serum progesterone value prior to delivery was 121 ng. per milliliter which was well within the standard deviation range in normal pregnancy.

6. Anencephalic. The maternal serum progesterone in an anencephalic pregnancy was 128, 180, and 132 ng. per milliliter at 36 to 37.5 weeks (Fig. 5), within the standard deviation range in normal pregnancy.

Comment

Serum progesterone measured by competitive protein-binding assay rises throughout pregnancy and reaches a peak at week 40 of gestation, in contrast to reports of falling serum progesterone during the last 4 weeks of pregnancy prior to labor.[27, 28] Differences in assay method, the use of the last menstrual period compared to the date of labor as a reference point, and cross-sectional compared to serial longitudinal study could account for differences in findings. However, the highest mean level of progesterone of 156 ng. per milliliter at 36 weeks by RIA[27] and 173 ng. per milliliter by competitive binding assay[28] are comparable to or even higher than mean levels of progesterone from 36 and 38 weeks' gestation in the present study. Although there was a fall in the mean serum progesterone in the last 4 weeks of pregnancy prior to labor, one third of the patients in that study showed little change in plasma progesterone until labor.[27]

The present study shows that serum progesterone does not appear to be a good index of fetal welfare in utero in high-risk pregnancies. Unlike serum unconjugated estradiol-17β, which was previously reported by Dawood and Ratnam[29] to be low in growth-retarded babies (No. 4 and 7 of Table II in present series), serum progesterone is unable to identify fetal-growth retardation in patients with hypertensive disorder of pregnancy. The wide day-to-day variation of serum progesterone in the same patient with a coefficient of variation of 22 per cent[30] and the intermittent release of placental steroid hormones accounting for the wide fluctuation in serum progesterone throughout the day in pregnant women with a maximum variation about the mean of up to 25.0 per cent,[31] detract from any potential value that serum progesterone might have in predicting placental function. In normal pregnancy, it is clearly seen that as pregnancy advances the scatter of serum progesterone levels becomes wider and there is up to a fivefold difference between the lowest and the highest values of serum progesterone found. This wide variation within the same patient throughout the day and from day to day and from patient to patient is more likely to be responsible for the poor value of serum progesterone in late pregnancy rather than the fact that progesterone is the product of maternal precursors synthesized solely by the placenta without fetal contribution. In this respect, human chorionic somatomammotropin (hCS), which is also synthesized solely by the placenta without fetal participation and

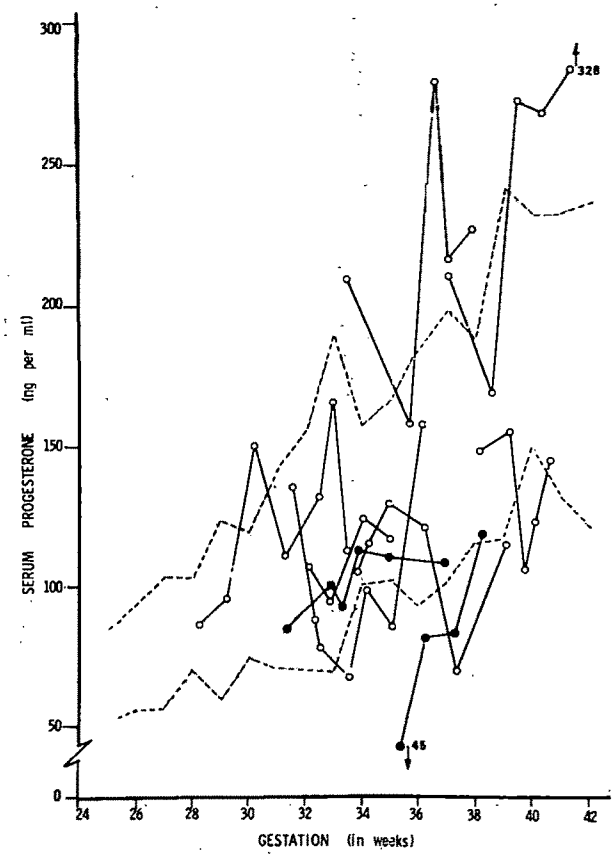


Fig. 2. Serial maternal serum progesterone concentration in nine patients with severe hypertensive disorder of pregnancy. Broken lines represent the standard deviation range for normal pregnancy. Black circles indicate pregnancies ending in birth of growth-retarded babies; clear circles indicate pregnancies ending in birth of babies with no growth retardation.

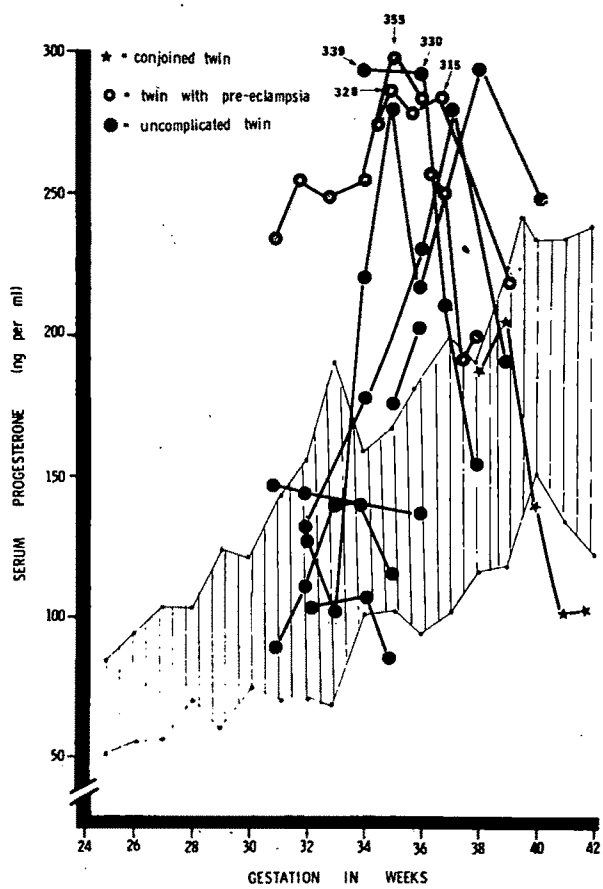


Fig. 3. Serial maternal serum progesterone concentration in 11 patients with twin pregnancy. Shaded area represents the standard deviation range for normal pregnancy. The conjoined twin (*) was a double-headed monster with a single trunk but two spines.

with much less fluctuation throughout the day than serum progesterone, is a satisfactory index of placental function.[32] Differences in the metabolism of progesterone in normal pregnant women when compared to pregnancies with low birth weight with or without hypertension further compound the difficulty in using serum progesterone as an index of placental function. The conversion rate of progesterone to pregnanediol is lower in disturbed pregnancies than in normal pregnancies.[33]

Although some earlier workers[16, 20] had found that plasma progesterone in the last trimester of multiple pregnancy gave high values in most cases, Greig and associates[21] attributed this to the size of the fetuses rather than the number of fetuses. Although superovulation in rabbits resulted in increased numbers of corpora lutea, normal fetuses, and total implantation, no increase in peripheral plasma progesterone was observed.[34] In all 11 twin pregnancies studied with or without hypertensive disorder of pregnancy, serum progesterone was similar to the normal pregnancy range up to weeks 33 or 34. Thereafter the levels were mainly higher than the standard deviation range. This rise appears to coincide with rapid fetal growth and, therefore, increased placental activity. However, this could also reflect increased demands in twin pregnancy on placental progesterone supply by fetal organs, namely the adrenals, for corticosteroid synthesis and this is fulfilled by increased progesterone synthesis by the placenta, which is usually larger in twin pregnancy than in single pregnancy. The single case of a double-headed monster with a single trunk and one pair of adrenal glands only would appear to support this, as the serial maternal serum progesterone was consistently within the normal standard deviation range for pregnancies with a single fetus. Fetal weight per se was unlikely to account for the serum progesterone finding in this particular case as the monster weighed more than 4,500 grams. The original intention of measuring serum progesterone in multiple

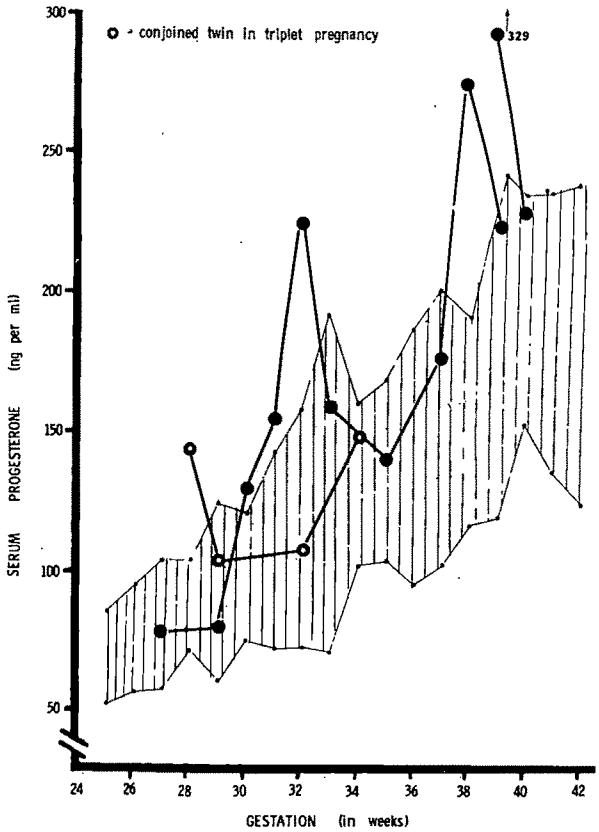


Fig. 4. Serial maternal serum progesterone concentration in three patients with triplet pregnancy. Shaded area represents the standard deviation range for normal pregnancy. The conjoined twin was a thoracoabdominopagus.

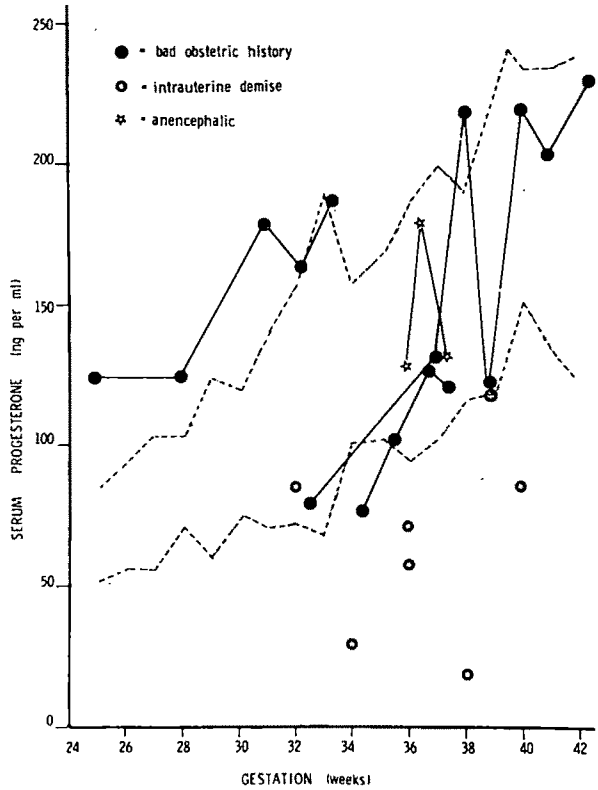


Fig. 5. Serial maternal serum progesterone concentration in three patients with poor previous obstetric history and one patient with anecephalic fetus and single maternal serum progesterone levels in seven patients with intrauterine fetal death. The broken lines represent the standard deviation range for normal pregnancy.

pregnancy was to establish serum progesterone levels in uncomplicated twin pregnancy as well as antenatal monitoring of placental hormonal activity in multiple pregnancy which carries a higher risk than in a pregnancy with a single fetus. This study points out the fallacy of using normal single pregnancy values for interpreting hormonal values in assessing placental function and this has also been recently demonstrated with urinary estriol in twin pregnancy.[35]

All the patients with twin pregnancy showed appreciable drops in serum progesterone after week 38 of gestation. In twin pregnancy, it has been suggested that the placental function begins to drop from week 38 onward, which is believed to correspond to a placental activity of 40 weeks in pregnancies with a single fetus, and it is possible that declining placental function may be responsible for the drop in serum progesterone. Nevertheless, in the three triplet pregnancies which had no maternal obstetric disease to account for placental dysfunction, serum progesterone concentrations were usually within the normal pregnancy range. It is difficult to explain this but the number of patients was small. Perhaps despite increased placental size the extra demands made by three fetuses for progesterone account for this.

Maternal serum progesterone was below the standard deviation range in five out of seven cases of intrauterine fetal death. However, except for two patients who had progesterone levels of 19 and 29 ng. per milliliter, the other five patients had serum progesterone concentrations which were compatible with normal pregnancy. Similar findings were noted in patients with severe pre-eclampsia who had subsequent intrauterine deaths.[18] Thus, serum progesterone is not of diagnostic value in intrauterine deaths nor could it predict impending fetal death. Cassmer[36] showed that urinary pregnanediol dropped by only 20 per cent after ligating the umbilical cord, thus reflecting the production of progesterone as long as viable trophoblasts or placenta persists. Unlike serum estradiol-17β, which was low in one of the three patients who had bad previous obstetric history[27] (No. 2, Table IV), serum progesterone was similar and within normal pregnancy range in all the three patients, although No. 2 (Table IV) had a small-for-dates infant that resulted in neonatal death.

The normal serum progesterone in the case of anencephaly was not unexpected and confirms the lack of significant fetal pituitary-adrenal participation in progesterone production in pregnancy.

This work was performed while the author was lecturer in obstetrics and gynecology at the University of Singapore, Kendang Kerbau Hospital.

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Assay of estriol-16α-(β-D-glucuronide) in pregnancy urine with a specific antiserum

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A rapid, direct radioimmunoassay for estriol-16α-(β-D-glucuronide) in pregnancy urine has been developed by use of immunogens in which the estriol glucuronide hapten is linked through positions 2 or 4 of ring A to bovine serum albumin or agarose gel. The resultant antibodies cross react less than 1 per cent with other estriol conjugates, estradiol conjugates, or unconjugated estrogens. Pregnanediol-3-glucuronide cross reacts less than 0.5 per cent. This high degree of specificity of the antibodies allows for a 10,000-fold dilution of pregnancy urine to be assayed directly without interference from other steroids or urinary constituents. Good linear correlation was obtained for urinary estriol glucuronide equivalents measured in the same subjects by our routine colorimetric method which separates and measures free estriol after hydrolysis. With an accelerated antibody-antigen equilibration of 20 minutes at 40°, 10 samples can be easily processed in less than 90 minutes. The method also allows for the evaluation of variations in the excretion pattern of one estrogen conjugate in normal and high-risk pregnancies.

ALTHOUGH estriol-16α-(β-D-glucuronide) is considered to be the major urinary estriol excretion product in human pregnancy,[1] there have been only two reports of its estimation by radioimmunoassay, neither of them specific for this one conjugate. In 1971, Gurpide and associates[2] observed that antibodies raised against estriol-16, 17-dihemisuccinate-BSA would bind estriol glucuronide. However, the assay was limited to the estimation of total estrogens since other free and conjugated estrogens competed equally as well as labeled estriol for the antibody-binding sites. More recently, Davis and Loriaux[3] reported a urinary assay for estriol-16-glucuronide based on an antiserum against an estriol-16α-glucuronide-BSA conjugate. The estriol glucuronide was attached to the protein through its carboxyl group and, although the resultant antiserum was considerably more specific than that of Gurpide and associates, labeled estriol was easily displaced from the antibodies by estradiol and to a lesser extent by estrone and estriol-17β-glucuronide.

The present report describes the production of an antiserum highly specific for estriol-16α-glucuronide and its use in a rapid, direct assay for this substance in pregnancy urine. Specificity was achieved by the use of two immunogens in which the estriol-16-glucuronide hapten was attached to BSA or agarose at positions(s) 2 and/or 4 of ring A. Antiserum was obtained which, when labeled with tritiated estriol-16α-glucuronide, cross reacted less than 1 per cent with estriol, estradiol, or their 3- or 17-glucuronides.

Materials and methods

Estriol, estradiol, and pregnanediol conjugates were obtained from Sigma Chemical Co., and AH-Sepharose-4B from Pharmacia. [6,9(n)-^{3}H] Estriol-16α(β-D-Glucuronide), 50 Ci. per mmol, was purchased from Amersham/Searle Co. This material was dissolved in 0.1M sodium phosphate, pH 7.6, and fractionated on a Sephadex-G-15 column. The counts eluted in the first two void volumes were discarded together with the last 10 per cent of the counts remaining on the column. This procedure reduced the assay blank, i.e., the counts "bound" in the absence of antiserum, to less than 1 per cent of the total (see below).

Estriol-6, 7-^{3}H(n), 53.1 Ci. per mmol, was purchased from New England Nuclear Corporation, and the

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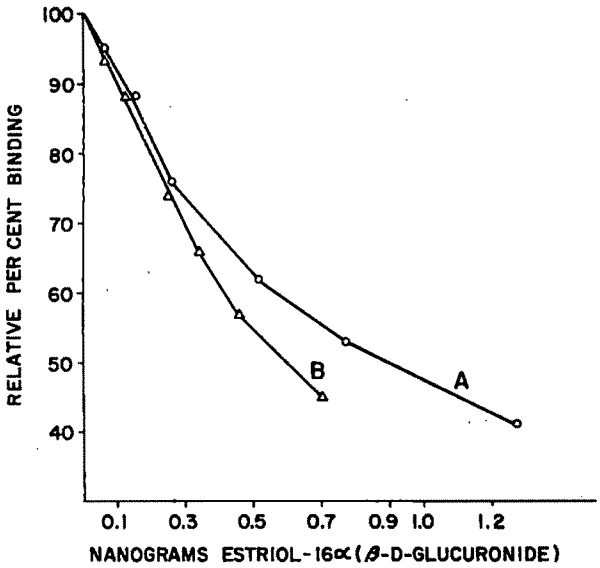


Fig. 1. *A*, Standard curve for ^{3}H-estriol-16α-glucuronide–labeled antiserum. *B*, Antiserum collected 1 month later. In the absence of unlabeled estriol glucuronide, about 25 per cent of the added counts were bound in both cases. See text for further details.

Table I. Specificity of the antiserum

Steroid	*Cross reaction** %
Estriol-16α-glucuronide	100
Estriol-17β-glucuronide	<0.5
Estriol-3-glucuronide	0.70
17β-estradiol-3-glucuronide	0.75
Pregnanediol-3-glucuronide	<0.5
Estradiol-17β-glucuronide	<0.5
17β-Estradiol	<0.5
Estriol	<0.5
Estrone	<0.5

*Per cent cross reaction was calculated as follows:

$$\frac{\text{Mass of estriol-16}\alpha\text{-glucuronide displacing 50 per cent of label}}{\text{Mass of steroid displacing 50 per cent of label}} \times 100.$$

organic reagents used for the synthesis of the immunogens were obtained from Eastman Kodak.

Preparation of agarose-estriol-16α-(β-D-glucuronide) immunogen. Bromoacetamidoethyl-agarose was prepared by reacting aminoethyl-Sepharose-4B with 0-bromoacetyl-N-hydroxysuccinimide.[4] This bromoacetyl product, from 1.2 Gm. of Sepharose AH-4B, was equilibrated with 0.1M sodium bicarbonate, pH 8.9, and suspended in the buffer to a total volume of 10 ml. To this suspension were added 10 mg. of estriol-16α-(β-D-glucuronide) labeled with a trace amount of [6,9(n)-^{3}H] Estriol-16α-(β-D-glucuronide) and dissolved in 6 ml. of bicarbonate with 2 ml. dioxane. The reaction was allowed to proceed for 4 days at room temperature, and after exhaustive washing it was determined that 7.7 per cent of the estriol counts were bound to the gel. Attachment was presumed to occur by an electrophilic alkylation reaction at positions 2 or 4 of the phenolic ring A of the steroid, although formation of an ether linkage through the 3-hydroxyl group might also occur to a limited extent.

Preparation of BSA-estriol-16α-(β-D-glucuronide) immunogen. Bromoacetyl-BSA was prepared by reacting the free amino groups of bovine serum albumin (Armour, Fraction 5) with 0-bromoacetyl-N-hydroxysuccinimide as follows: 2 mmoles of freshly synthesized bromoacetylsuccinimide in 15 ml. of dioxane were added to 15 ml. of an aqueous solution of 200 mg. of BSA, pH 8.1. The resultant solution, pH 3.5, was adjusted to 7.8 with sodium hydroxide, and after standing for 1 hour at room temperature was dialyzed against 3 × 1 L. of distilled water.

A 16 mg. quantity of estriol glucuronide containing 1 μCi of tracer steroid was added to 4 ml. of 5 per cent bicarbonate and solubilized with 2.8 ml. of dioxane. This solution was added to one-fourth of the above bromoacetyl-BSA dialysate and the reaction allowed to proceed for 92 hours at room temperature. The extent of reaction, as estimated by the nondialyzable counts attached to BSA, was 13 per cent in 3 hours; 23 hours, 20 per cent; 47 hours, 29 per cent; 71 hours, 30 per cent; 92 hours, 33.6 per cent. Taking 65,000 as the molecular weight of BSA, this corresponds to about 23 of the 60 available amino groups per mole conjugated with estriol glucuronide.

Immunization of rabbits. Each of two female estrus rabbits, initially weighing about 3 kilograms, was given weekly multiple subcutaneous injections of an emulsion of 0.5 ml. Freund's Complete Adjuvant with 0.5 ml. of an aqueous suspension of 50 mg. of the agarose-estriol glucuronide gel. After 8 weeks, immunization of one rabbit, which had the highest antibody titer, was continued with weekly injections of 2 mg. of the BSA-estriol glucuronide immunogen with Freund's Adjuvant for an additional 4 weeks. Administration of 2 mg. of the BSA-estriol glucuronide without adjuvant was continued every other week to maintain antibody production.

Separation of antibody-bound ^{3}H-estriol glucuronide. This was accomplished with microdisposable columns containing Sephadex-G-15 made from 15 by 0.7 cm. Pasteur pipets. The pipets were plugged with glass wool and 1.8 ml. of a rapidly stirring suspension of Sephadex-G-15 introduced into each. This gives a bed height of about 1.5 cm. with the use of

a suspension of swollen gel to water ratio of 1:3.2 (v/v). A 100 μl aliquot of an equilibrated solution of diluted antiserum and labeled estriol glucuronide in 0.1M sodium phosphate, pH 7.6, was allowed to completely penetrate the gel bed and immediately eluted with 500 μl of 0.15M sodium chloride. The total eluent containing the bound steroid was collected in scintillation vials and counted in a toluene scintillation solution containing 33 per cent by volume of Triton-X-100. Counting efficiency was about 35 per cent for 600 μl of aqueous solution solubilized with 5 ml. of counting fluid. Under these conditions the unbound steroid is almost entirely retained by the column: less than 1 per cent of the total counts are eluted in the absence of antiserum. The entire procedure can be carried out on 10 samples in less than 10 minutes.

Direct assay of pregnancy urine. An aliquot of a 24 hour pregnancy urine was diluted 500:1 with distilled water and 10 μl were assayed in 200 μl of sodium phosphate, pH 7.6, containing enough antiserum to give 20 to 30 per cent binding with 5,000 c.p.m. of ^{3}H-estriol-16α-glucuronide. A standard curve containing 50 to 1,000 pg. of unlabeled estriol glucuronide was run with each assay. After equilibration for 20 minutes at 40°, or about 2 hours at room temperature, the bound steroid in a 100 μl aliquot was separated and counted as above.

Colorimetric estriol assay. Estriol was assayed in pregnancy urine essentially by the method of Greene and Touchstone,[5] except that a trace amount of tritiated estriol was added before hydrolysis for calculation of procedural losses. The assay involves a 15 minute hydrolysis in boiling 1.5M HCl, followed by purification of the liberated estriol by liquid-liquid partition and alumina chromatography. The purified estriol is then determined colorimetrically by reaction at 150° with p-phenolsulfonic acid in 85 per cent phosphoric acid. The procedure separates estriol from all of the other major estrogens and interference from other urinary solutes is minimal. Procedural losses amount to about 40 per cent, mainly due to retention of estriol on the alumina column. The reliability of the assay in the management of high-risk pregnancies has been firmly established in this laboratory over the past 5 years, during which over 2,200 determinations have been carried out.

Results

Properties of the antiserum. The high degree of specificity of the antiserum is illustrated by the data in Table I. It is evident that none of the major estrogens or their glucuronide conjugates will appreciably displace estriol-16α-glucuronide from these antibodies. Pregnanediol-3-glucuronide, the only steroid whose concentration in pregnancy urine approaches that of estriol glucuronide, is also inactive. Under conditions in which 50 per cent binding of ^{3}H estriol-16α-glucuronide occurred, which was initially at a serum dilution of 50- to 100-fold, less than 0.2 per cent binding of ^{3}H-estriol (53.1 Ci. per mmol) was observed.

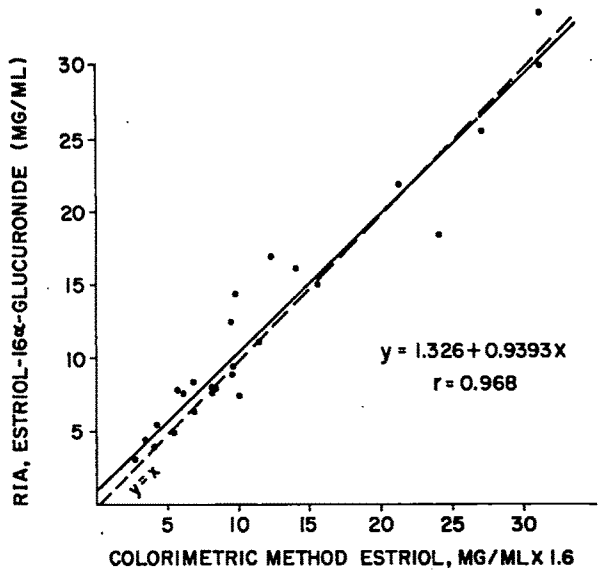


Fig. 2. Correlation between values for estriol (expressed as estriol glucuronide) in hydrolyzed urine obtained with the colorimetric Greene-Touchstone procedure (abcissa) and the present radioimmunoassay (ordinate). Dashed line is the line of identity, $x = y$.

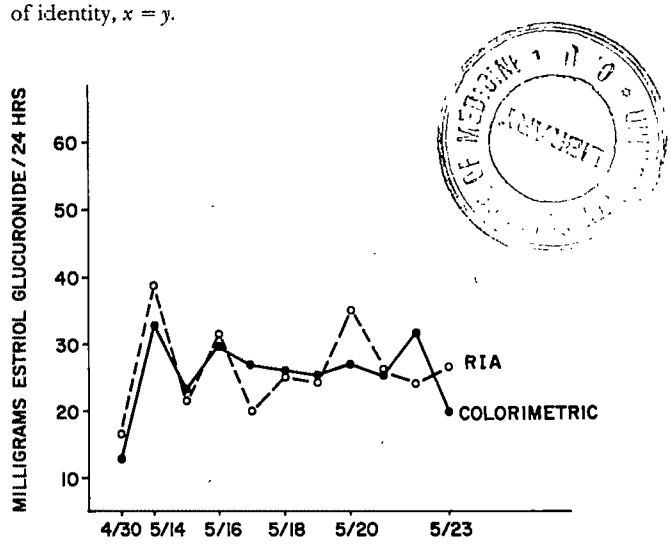


Fig. 3. Correlation between values for estriol-16α-glucuronide (present radioimmunoassay) and estriol by the colorimetric procedure (expressed as estriol glucuronide) for eleven 24 hour urines from a diabetic patient.

The antibodies also easily distinguish between the 16α and 17 β estriol glucuronide conjugates.

The two standard curves in Fig. 1 illustrate the sensitivity of the antiserum as well as the increase in this sensitivity with continuing immunization. As shown by curve *A*, 880 pg. of estriol glucuronide were initially required for 50 per cent displacement of label, as compared to 600 pg. with serum drawn 1 month later (curve *B*). The lower limit of sensitivity of the assay is better than 60 pg. of estriol glucuronide, which commonly gives a displacement of 6-10 per cent.

Immunization of the rabbits with the agarose-E_3G immunogen gave an initial antibody response followed by a decline in production despite continued injections. Because of the suspicion that hyperimmunization had occurred, the BSA-E_3G immunogen was then employed, giving good results with one rabbit. The antiserum from this rabbit continues to increase slightly in titer and sensitivity. No change in specificity has been observed, although it has been our experience, contrary to general opinion, that specificity will, in some cases, increase with continued immunization.[6, 7]

Assay of estriol-16α-glucuronide in pregnancy urine. Under the assay conditions described in Methods, neither male urine nor normal female urine causes any displacement of labeled estriol glucuronide from the antiserum. The final dilution of urine in the assay mixture is about 10,000:1. Dilutions of a single urine sample to 10,000, 14,000, 20,000, and 40,000:1 gave assay values of 30.1, 30.8, 33.6, and 32.5 μg of estriol glucuronide per milliliter, respectively. The within-assay coefficient of variation as defined by

$$CV = \left[\frac{Ed^2}{2n}\right]^{\frac{1}{2}},$$

for n = 5 (10 samples) was 6.8 per cent; the between-assay variation was 17.7 per cent.[8]

The data in Fig. 2 shows the correlation between values for estriol-16α-glucuronide obtained by radioimmunoassay and total estriol as determined by the Greene-Touchstone colorimetric assay for a number of late pregnancy urines. Values obtained by the colorimetric assay are corrected for procedural losses and have been converted to an equivalent weight of estriol glucuronide by multiplying by the ratio of molecular weights (464.5/288.4 = 1.6). The regression line (Y = 1.326 + 0.9393 X) indicates that the radioimmunoassay values tend on the average to be slightly higher than those obtained by the colorimetric procedure. The coefficient of correlation (r) is calculated to be 0.968. A more intensive statistical analysis of these data[3] was not attempted, since it is felt there exists a sufficiently good correlation to warrant further evaluation of the method in clinical situations with suspected fetal jeopardy.

Ten consecutive 24 hour urine samples (and one baseline sample) from an 18-year-old class B diabetic patient were assayed with both the colorimetric and radioimmunoassays. The results, illustrated in Fig. 3, again demonstrate an essential close agreement between the two methods. Upon confirmation of a mature L/S ratio, the patient was delivered of a viable infant by cesarean section on May 23, at 37 weeks.

Comment

The colorimetric estriol assay routinely employed in this laboratory measures mainly free estriol and some closely related minor estrogens, such as 16-epiestriol, after release by hydrolysis. The 15 minute acid treatment, however, is a compromise for time and does not result in complete hydrolysis of the estriol conjugates, nor does the estriol tracer correct for this unhydrolyzed fraction. The proportions of the various major estriol conjugates in term pregnancy urine have been estimated as follows: estriol-16α-glucuronide, 68 per cent; estriol-3-glucuronide, 23 per cent; estriol-3-sulfo-16α-glucuronide, 6.5 per cent; estriol-3-sulfate, 2.5 per cent.[9] These proportions apparently vary progressively with advancing pregnancy in some subjects but not others. The presently observed close correlation between the concentration of estriol-16α-glucuronide and total hydrolyzed estriol is taken to indicate that the unhydrolyzed estriol fraction is relatively constant, and comprises about 30 per cent of the total estriol conjugates, assuming the above percentages and the assay specificity.

The main advantage afforded by use of the present antiserum, aside from the obvious time-saving factor, is the opportunity to determine how the variation in one particular urinary estriol conjugate, namely estriol-16α-glucuronide, relates to fetal well-being and the clinical course of various types of high-risk pregnancies. In some diabetic pregnancies, for instance, it has been estimated that the various estriol conjugates represent less than 50 per cent of the total estrogens.[10] What relationship might the variation of one conjugate have with the outcome of such pregnancies? Such evaluations are now under way in this laboratory in expectation that focusing on a single parameter might yield more, or at least different information from that afforded by considerations of the average or total estriol or estrogen picture.

The author wishes to thank Mrs. Ruth Higgs for her technical assistance.

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The effect of epidural anesthesia on uterine activity and blood pressure

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Because of the unresolved controversy regarding the effect of epidural anesthesia upon uterine contractility, it was decided to study its effect on a small number of patients. Intrauterine and intra-arterial continuous pressure, continuous fetal heart rate, and maternal heart rate recordings were obtained from at least 20 minutes before administration of the epidural anesthetic until complete dilatation in these patients. Nineteen patients were in spontaneous labor, and 18 had labor stimulated with oxytocin. Plain lidocaine, 1 or 1.5 per cent, was used in 12 patients (30 observations), and lidocaine with epinephrine, 1:200,000 was used in 26 patients (51 observations). Uterine contractions were calculated in Montevideo units for 60 minutes following the epidural anesthetic. The changes, if any, were compared in both groups. There was a significant decrease in uterine activity when epinephrine was added to the anesthetic solution, mainly a lessening of intensity. There were comparable decreases in systolic/diastolic blood pressure in both groups and compensatory tachycardia. In one case, severe hypertension was observed following administration of lidocaine epinephrine. It was concluded that the addition of epinephrine to the anesthetic solution predictably produces diminution of uterine activity, and it does not give "cardiovascular support" to the laboring patient.

WHILE A NUMBER OF studies show that epidural anesthesia during labor is safe for the mother and has no untoward effects on the offspring,[21] its effect on uterine activity remains a matter of controversy. Most obstetricians expect some diminution in uterine activity, but this impression has not been clarified by studies to date. Decreased activity has been reported in some communications,[14, 19, 20] whereas others[9] observed an acceleration in labor. The level of uterine activity has not been related to therapeutic doses and serum levels of anesthetic solutions[18] or the type of anesthetic solution used.

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This study was initiated to determine whether one suggested variable—the addition of epinephrine to the anesthetic solution—may be a contributing factor in altering uterine dynamics after institution of lumbar epidural anesthesia during labor. We also examined the effects of plain as well as epinephrine-added anesthetic solution on the maternal cardiovascular system.

Material and methods

Thirty-seven normal patients at or near term admitted to the delivery suite of the Chicago Lying-in Hospital were included in this study. Nineteen patients were in spontaneous labor while the remainder had labor induced with synthetic oxytocin or had enhancement of labor prior to, or during the period of, anesthesia. There were 22 nulliparous and 15 multiparous patients. All infants were in cephalic presentation except for one breech. There was one pair of twins, the first in cephalic presentation.

All were successfully given continuous lumbar epidural anesthesia started within the range of 3 to 8 cm. of cervical dilatation. All the patients except two completed a normal first stage of labor and were

subsequently delivered by the resident staff. Of the two delivered by cesarean section, one patient had labor terminated because of failure of labor to progress and cephalopelvic disproportion; the other was delivered abdominally because of an inadequate pelvic outlet, after she had progressed to complete cervical dilatation.

In all patients continuous intrauterine pressure tracings were recorded throughout the period of anesthesia according to the Alvarez and Caldeyro technique of transabdominal intrauterine catheterization[6] or by transvaginal passage of a catheter into the uterine cavity. The fetal heart rate was monitored continuously with an electrode attached to the presenting part, which was the scalp in all cases except in the breech presentation, when attachment was made to a heel. In 12 patients, continuous blood pressure and heart rate recordings were made by catheterization of the left femoral artery[6]; the pulses from this were fed into a cardiotachometer to give continuous heart rate recordings. The analgesia was given through a polyethylene catheter placed in the epidural space in the region of the third to fifth lumbar vertebrae. Lidocaine, 1 or 1.5 per cent, was used in all cases; plain lidocaine was used in 12 patients in whom 30 observations were made, while lidocaine with epinephrine, 1:200,000, was used in 26 patients in whom 51 observations were made. The dose of epinephrine with each administration ranged from 20 to 50 mcg. One patient had both plain as well as epinephrine-added lidocaine. Table I shows the distribution of patients in the control and test groups who were in spontaneous labor or had oxytocin-stimulated labor.

A base-line period of at least 20 minutes of recording preceded the injection of the anesthetic. A test dose of 30 to 60 mg. of plain lidocaine or lidocaine with epinephrine was injected, and then an additional dose of 60 to 100 mg. was added to raise the sensory blockade to the level of the tenth thoracic vertebra. The changes in uterine contractions calculated in Montevideo units were determined in the following 60 minute period. Repeat doses were included in the study only when there was a return to a steady preanesthetic base-line following the initial dose. Changes known to influence uterine contractility, such as rupture of the membranes and changes in the infusion rate of oxytocin were avoided; when this was not possible, the patient was excluded from the study.

In the arterial blood pressure and heart rate tracings, control values before anesthesia were compared with the values recorded after a good level of analgesia was established. All readings were taken in the intervals between contractions, since relatively great hemodynamic changes are known to occur during the active phase of contractions.[13]

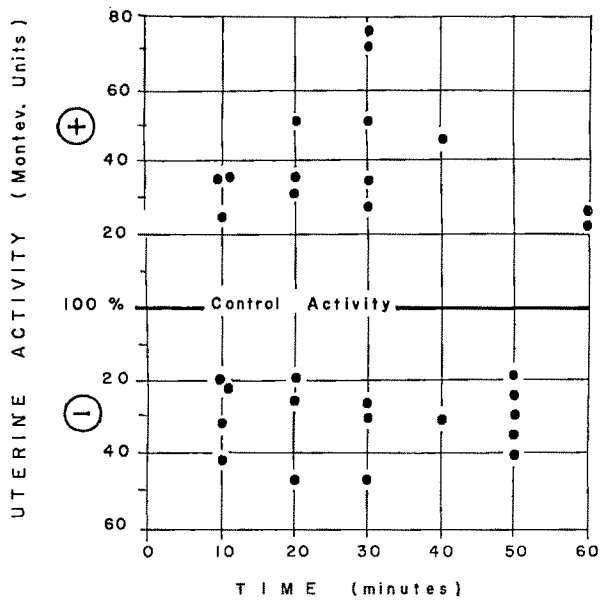


Fig. 1. Maximum relative change in uterine activity, from preanesthetic base line, following administration of anesthetic in group given plain lidocaine (30 observations). The preinjection activity was taken as 100 per cent. The subsequent values were calculated at 10 minute intervals, and the maximum change was plotted at the corresponding time.

Table I. Distribution of patients in spontaneous and oxytocin-stimulated labor in the two groups

Anesthetic solution	*Spontaneous labor*	*Oxytocin-stimulated labor*
Plain lidocaine	6	6
Lidocaine with epinephrine	13	13

Results

Uterine activity. From the preanesthetic base-line, the activity following institution of the epidural block was determined at ten-minute intervals for the following 60 minutes, and these levels were expressed in per cent activity relative to the base-line. Figs. 1 and 2 show the maximum changes in activity (either an increase or a decrease) which occurred after injection of either plain lidocaine or lidocaine with epinephrine and the time at which these occurred. There were 30 observations in the group in whom plain lidocaine was used, with an increase in activity in 14 cases and a decrease in 16 cases. In the group who had epinephrine-added lidocaine, there were 51 observations, with an increase in activity in 12 cases and a decrease in 39 cases.

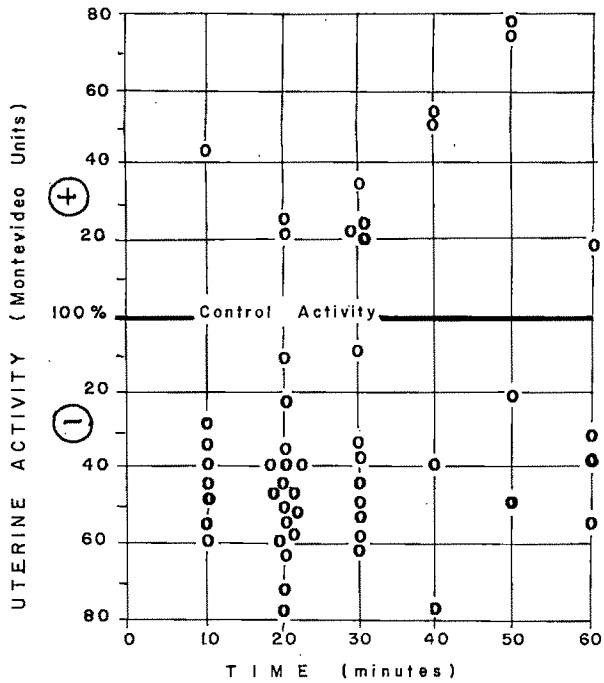


Fig. 2. Maximum relative change in uterine activity, from preanesthetic base line, following administration of anesthetic in group given epinephrine-added lidocaine (51 observations). The preinjection activity was taken as 100 per cent. The subsequent values were calculated at 10 minutes intervals, and the maximum change was plotted at the corressponding time.

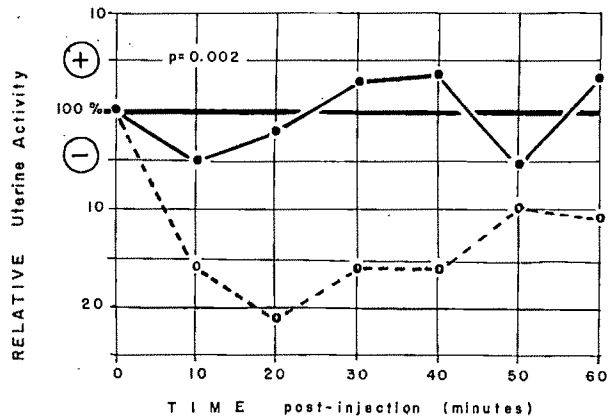


Fig. 3. Mean values of uterine activity after epidural administration of lidocaine (●—●) or lidocaine with epinephrine (O--O) for all individual observations calculated every 10 minutes, for both groups of patients.

The relative changes in activity shown in Fig. 3 are the averages for all individual observations calculated every ten minutes. These are the means of the values obtained for each individual case following administration of the drug. The relative activity throughout the 40 minutes following the epidural injection was then calculated for each case, giving an average of activity for this period. These values in the two study groups were then compared and subjected to statistical analysis. There was a significant decrease in uterine activity when epinephrine was added to the anesthetic solution ($p = 0.002$). The statistical analysis was made with the two-tailed test, and Welch's degrees of freedom were utilized.

The lower levels of uterine activity in the group who had epinephrine-added lidocaine were mainly due to a decrease in intensity which occurred in all cases, whereas a decrease in frequency was not observed in all cases in which a net decrease in activity occurred (Fig. 4). Initial doses of epinephrine-added anesthetic solution produced the most notable and profound decreases in uterine activity, this being less marked in the repeat doses. The level of uterine activity in cases in which epinephrine was used tended to stay below the preinjection levels up to 60 minutes after administration of the anesthetic, while in cases in which plain lidocaine was used there was either the existing level or an increase in activity at the end of the 60 minute period of analysis (Fig. 3). For the group who had epinephrine-added in the majority of cases the maximum decrease in uterine activity occurred within 30 minutes of administration of the anesthetic (Fig. 2). Changes in the group given plain lidocaine were spread out over the 60 minutes following administration (Fig. 1).

Cardiovascular effects. Tables II, III, and IV show the different effects of the induction of lumbar epidural anesthesia on blood pressure and heart rate which may occur.

There were consistent though modest drops in blood pressure about five minutes after the therapeutic dose of the drug was given, with a corresponding increase in the heart rate. These small drops in blood pressure and increases in heart rate occurred in both groups of patients, and one such case is illustrated in Fig. 5. After comparison of the values shown in Tables III and IV, it may be seen that there is little quantitative difference in the changes in blood pressure and heart rate in the two groups of patients. The average decrease in systolic and diastolic blood pressures in the group who had plain lidocaine were 9 and 6 mm. Hg, while these values were 10 and 9 mm. Hg, respectively, for the group given epinephrine-added lidocaine. The average increase in heart rate was 18 beats per minute for the control group (lidocaine only) and 22 beats per minute for the test group (lidocaine with epinephrine).

The most profound drop in blood pressure occurred in a patient who had a dose of 50 mg. of lidocaine with

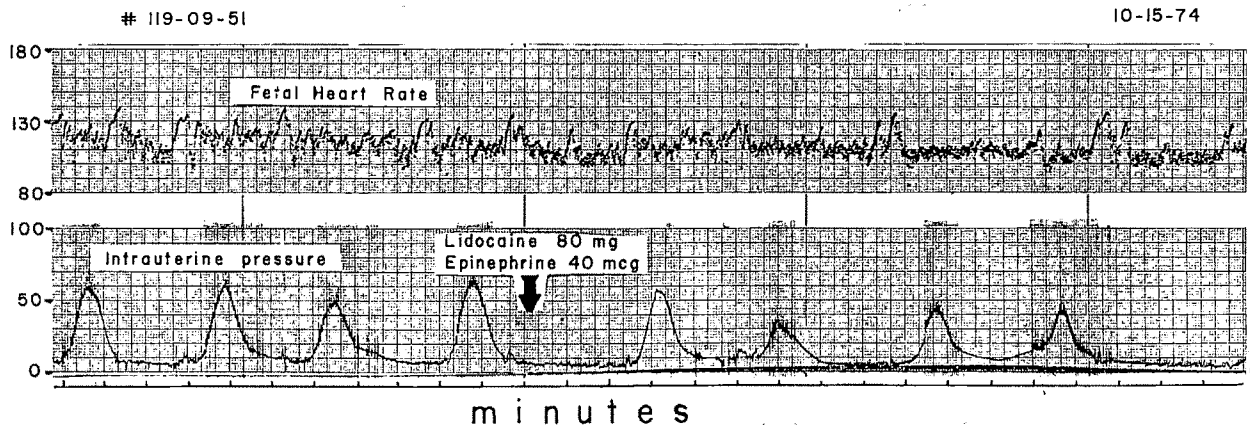


Fig. 4. Continuous fetal heart rate and intrauterine pressure recording in a multiparous patient at 4 cm. dilatation with ruptured membranes, receiving oxytocin at 10 mU. per minute. Uterine contractility rapidly decreased after epidural injection of lidocaine containing 40 mcg. of epinephrine because of a decrease in intensity. The frequency was practically unchanged during the 15 minutes after injection.

Table II. Average values of changes in blood pressure and heart rate after epidural anesthesia in the two groups

Anesthetic solution	*No. of observations*	*Preanesthesia*		*Postanesthesia*	
		Blood pressure	*Heart rate*	*Blood pressure*	*Heart rate*
Plain lidocaine	19	106/56	87	95/50	105
Lidocaine with epinephrine	21	112/58	90	102/49	112

25 mcg. of epinephrine through the epidural catheter with the patient in the supine position. The hypotension occurred six minutes after injection, and analgesia was demonstrated for the contraction following this episode of hypotension (Fig. 6). Anesthesia to the level of the eleventh thoracic vertebra was demonstrated minutes after injection of the anesthetic solution. Correction of hypotension was obtained by changing the patient's position to lateral recumbency. No hypertensive drugs were used in this patient.

In the one patient with a twin pregnancy, the cardiovascular parameters were not monitored continuously though frequent manual determinations of blood pressure showed a fall in diastolic levels of 40 to 50 mm. Hg. Despite rapid intravenous administration of five per cent dextrose in normal saline solution and turning the patient to one side, the diastolic pressure did not improve, even after the administration of 5 mg. of ephedrine intravenously.

There was one unexpected response to administration of lidocaine with epinephrine for epidural anesthesia (Fig. 7). This patient suffered subjective symptoms of severe occipital headache simultaneous with a sharp increase in blood pressure from preanesthetic levels. Two two phenomena were noticed 60 seconds following the beginning of the injection of the drug through the epidural catheter. The blood pressure declined rapidly to hypotensive levels, stabilizing to preanesthetic levels after 15 minutes. The headache also subsided, and no further intervention was necessary.

Continuous fetal heart rate monitoring was done in all cases and indicated that maternal hypotension may be associated with changes in the fetal heart rate only when it is maintained for some time. Rapid correction of the transient hypotension recorded in this study would prevent the appearance of fetal heart rate changes attributable to hypoxic conditions.

Comment

Uterine activity. This study showed a significant decrease in uterine activity in the first stage of labor following lumbar epidural analgesia induced with epinephrine-added lidocaine when compared with a control period of uterine activity before injection. This decrease was not seen in a control group of patients in

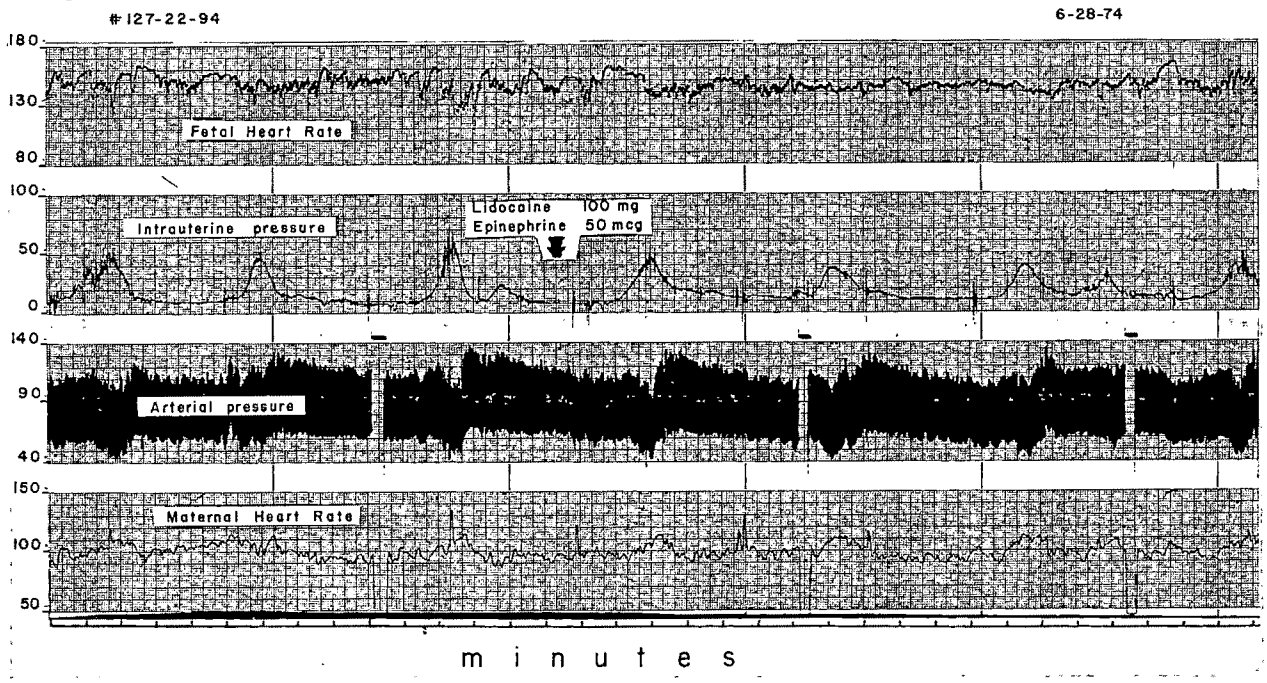


Fig. 5. Continuous recording of fetal heart rate, intrauterine pressure, arterial pressure, and maternal heart rate in a patient with enhanced labor. The test dose followed by the full dose (at arrows) produced only a modest drop in blood pressure and no tachycardia. There was a transient diminution in uterine activity. The increase in fetal heart rate occurred during a pelvic examination.

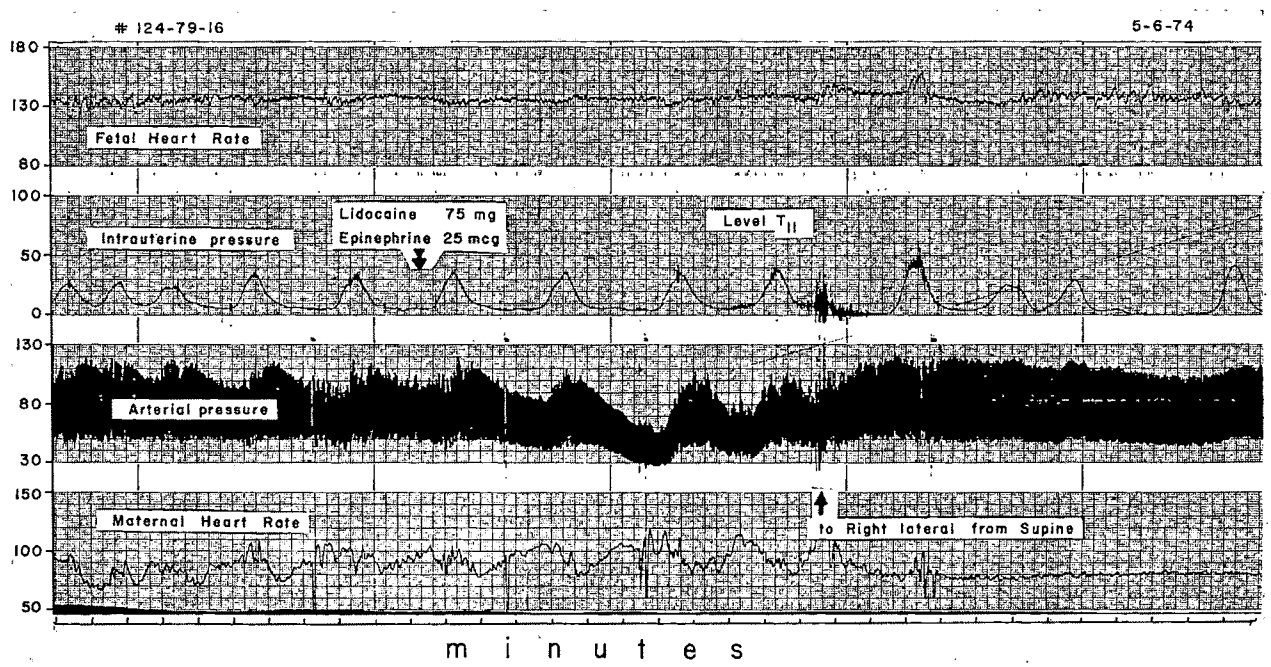


Fig. 6. Continuous fetal heart rate, intrauterine pressure, arterial pressure, and maternal heart rate recordings in a primigravid patient at 4 cm. dilatation with intact membranes. Severe hypotension occurred five minutes after the injection of 75 mg. of lidocaine with 25 mcg. of epinephrine (test dose) and was corrected by turning the patient to her side. Note the absence of changes in the fetal heart rate; fluctuation in blood pressure and maternal heart rates was absent when the patient turned to lateral position.

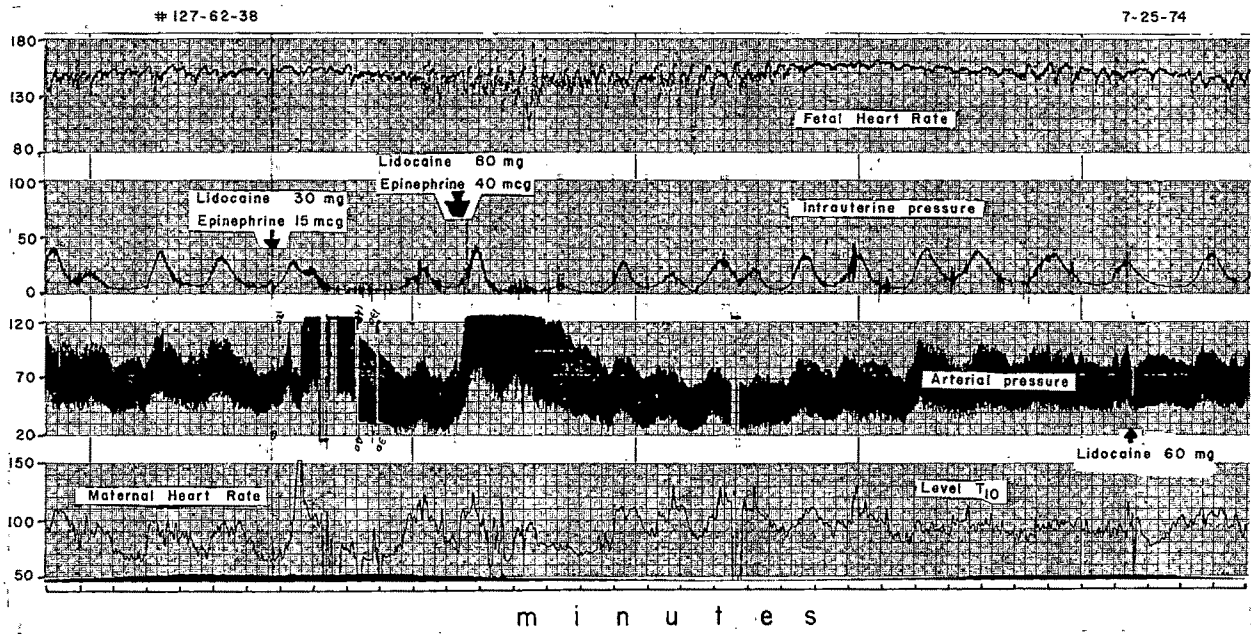


Fig. 7. Continuous recordings of the fetal heart rate, intrauterine pressure, arterial pressure, and maternal heart rate in a young primigravid patient following epidural injection of 30 mg. of lidocaine with 15 mcg. of epinephrine, and five minutes later 80 mg. of lidocaine with 40 mcg. of epinephrine, showing a sharp increase in blood pressure from preanesthetic levels of 80/50 to a systolic pressure of greater than 130 and a diastolic pressure of 82 mm. Hg. The recording ranges were changed as shown in order to pick up the maximum values. Note the subsequent hypotension (72/35) and tachycardia (up to 120) following this short episode of hypertension and occipital headache. Uterine activity was increased following the epidural injection, and fetal heart rate showed a transient increase. At the extreme right of the figure, another injection of plain lidocaine, 60 mg., did not have any hemodynamic effect.

whom plain lidocaine alone was administered. Comparable results were reported by Noriega Guerra and associates[15] in a group of patients given the anesthetic without epinephrine.

Similar findings have been reported by Craft and colleagues[10] in a study consisting of patients who all had labor induced electively with oxytocic drugs. They also reported a significant diminution of uterine forces by lidocaine with epinephrine compared to lidocaine alone during the first 20 minutes but not during the second 20 minutes following epidural administration. The present study examined the cumulative activity over the 40 minute period following anesthesia and was not confined only to induced labor. Gunther and Bauman[11] studied the duration of labor in a large group of patients given mepivacaine only and lidocaine with epinephrine for caudal analgesia. They found that the first stage of labor was significantly prolonged in the patients who received epinephrine-added medication, although they did not measure uterine activity directly as was done in this study.

A more detailed analysis of each case in the present study elicited two additional facts. When an increase in uterine activity occurred in the epinephrine-added group, it was, in most cases, in the late first stage of labor (cervical dilatation, 7 cm. or greater). The finding that repeat doses of epinephrine-added lidocaine did not produce as predictable and as marked a decrease in uterine activity as the initial dose should not be surprising. Pose and co-workers[16] found that epinephrine administered intravenously at 5 to 10 mcg. per minute caused a significant decrease in uterine activity, but, when the infusion was later increased from 10 to 20 mcg. per minute, no further effect was seen on the activity of the uterus.

The interpretation of biological phenomena resulting from systemic absorption of drugs from the epidural space must be done with caution. Vascular uptake is probably accomplished by blood vessels of the peridural space. The most important of these are consitutents of the internal vertebral venous plexus which is a primitive valveless system with connections to the superior vena through the azygos vein. In late pregnancy, where caval flow may be intermittently

Table III. Individual blood pressure changes in the group given plain lidocaine

Patient initials and Dose No.	*Original blood pressure recording (mm. Hg)*	*After epidural analgesia*	*Reduction (systolic/ diastolic)*
B. J.			
1	116/70	96/48	20/22
2	110/60	94/50	16/10
3	92/54	86/50	6/4
4	110/66	96/54	14/12
K. B.			
2*	94/52	84/48	10/4
3	96/52	96/52	0/0
4	102/56	90/54	12/2
5	96/54	96/54	0/0
S. B.			
1	122/58	96/58	26/0
2	126/60	126/50	0/10
3	128/54	126/54	2/0
R. M.			
1	98/54	92/46	6/8
2	100/56	100/56	0/0
3	96/54	96/50	0/4
D. B.			
1	86/48	80/46	6/2
2	115/55	76/44	39/11
3	105/55	85/50	20/5
D. S.			
1	106/50	98/44	8/6
2	112/62	86/46	28/16

*One patient had an initial dose of lidocaine with epinephrine and was thereafter maintained with plain lidocaine, because of an adverse cardiovascular response to the first injection (see "Comment").

Table IV. Individual blood pressure changes in the group given lidocaine with epinephrine

Patient initials and Dose No.	*Original blood pressure recording (mm. Hg)*	*After epidural analgesia*	*Reduction (systolic/ diastolic)*
P. C.			
1	112/60	102/50	10/10
2	112/60	100/50	12/10
3	108/60	108/46	0/14
4	110/64	110/58	0/6
5	124/72	112/64	12/8
S. H.			
1	130/50	110/50	20/0
2	112/64	102/50	10/14
3	110/62	100/50	10/12
4	108/60	106/54	2/6
5	112/62	110/58	2/4
6	132/74	112/62	20/12
D. S.			
1	94/52	66/28	28/24
2	102/52	100/46	2/6
3	104/60	90/48	14/12
4	108/56	98/44	10/12
D. F.			
1	125/50	115/45	10/5
2	138/50	120/50	18/0
3	110/48	102/42	8/6
S. H.			
1	95/60	95/50	0/10
L. T.			
1	110/52	104/46	6/6
K. B.			
1	100/60	76/40	28/20

obstructed, these veins are markedly distended and occupy a large proportion of the spinal canal.

Local anesthetic appears in the venous blood of man within a few minutes of injection in the epidural space and reaches maximum levels in 10 to 30 minutes, depending on the diffusion characteristics of the drug concerned.[4] This problem of vascular uptake seems to be particularly unpredictable in repeat doses of epinephrine-added anesthetic solutions administered into the epidural space and would be one uncontrollable variable affecting many aspects of the epidural anesthetic action.

Examination of the changes in uterine activity and cardiovascular responses which occurred in this study suggest not only that epinephrine is absorbed from the epidural space but also that its absorption is also dependent on the same factors which limit absorption of local anesthetic agents. Differing rates of uptake from the epidural space may account for the failure of uterine activity to return to preanesthetic levels in most cases where epinephrine is used. It may also account for the variation in the levels of postepidural uterine activity as well as the variation in the interval of time following administration at which the maximum decrease occurs.

The same mechanism may explain the observation by Rucker[17] that caudal anesthesia usually slowed labor when 330 mcg. of epinephrine in a concentration of 1:120,000 was added to the anesthetic solution but labor was unaffected when the epinephrine was omitted. Smaller concentrations of epinephrine and volumes of anesthetic solutions have been advocated [2, 4, 5, 12] as a means to prevent this diminution in uterine activity. However, Gunther and Bauman[11] reported a prolongation of first-stage labor when 75 to 100 mcg. of epinephrine were injected into the caudal space in a large series of patients while this did not occur in a comparable group who did not receive epinephrine. In this study, epinephrine doses as small as 20 mcg. caused a diminution in uterine activity when administered with the anesthetic solution to produce anesthesia.

Therefore, these various observations suggest that the added epinephrine, rapidly absorbed into the vascular system, may be the responsible factor causing the predictable diminution of uterine activity when it is added to the epidural anesthetic solution.

Cardiovascular. The cardiovascular effects observed in this study are not unlike those known to occur in response to conduction anesthesia. The maternal

hypotension, tachycardia and fluctuations which occur reflect the tendency of the pregnant woman to be somewhat more labile than the nonpregnant individual. The direct effects of epidural anesthesia may be a combination of fall in cardiac output from sympathetic blockade and smooth-muscle depression, vascular absorption of local anesthetic agents, and, when epinephrine is added, beta-receptor stimulation from vascular absorption, leading to a rise in cardiac output and a fall in peripheral resistance.

The patient who had a hypertensive episode and occipital headache following initial epidural injection of lidocaine with epinephrine was thereafter maintained in a good state of analgesia by further injections through the original epidural catheter, although no epinephrine was added to the anesthetic solution from then on. No further increases in blood pressure were seen with subsequent plain lidocaine epidural administration, and delivery of a healthy infant was accomplished uneventfully, while the patient herself did well in the postpartum period. Therefore, inadvertent intravenous injection may be ruled out; the hypertension recorded was more probably the result of rapid vascular absorption of epinephrine from the epidural space. On review of the patient's history, no signs or symptoms of pre-eclampsia could be elicited, and there was no evidence to indicate sensitization of the cardiovascular system to sympathomimetic drugs. This view, that the epinephrine in the anesthetic solution used in epidural anesthesia is responsible for the increased cardiovascular changes, has been advanced by Bonica and associates.[3]

In a recent study, Akamatsu and associates[1] found marked alterations in cardiovascular function during administration of epidural anesthetic solutions containing epinephrine. Methods of therapy necessary to correct hypotension including left uterine displacement, intravenous fluids, pressure boot inflation, and intravenous ephedrine were all utilized. They report that, despite these measures, marked variation in hemodynamic instability persisted throughout operation (cesarean section); instability was not observed in patients given epidural anesthesia without epinephrine. Peripheral vascular effects of absorbed epinephrine contained in the anesthetic solution were presumed to cause the difference in cardiovascular response. It has been shown that the pregnant patient is extremely sensitive to epinephrine and responds with significant hypotension.[16] Therefore, reiteration of the possible exacerbation in hemodynamic instability which may occur when epinephrine is added to epidural anesthetic solutions seems appropriate after appraisal of the data gleaned from this study. These observations do not support the commonly accepted premise that addition of epinephrine to anesthetic solutions in conduction anesthesia prevents, or minimizes, the undesirable cardiovascular effects of sympathetic blockade.

Effective methods of combating hypotension following conduction anesthesia, including maintenance of the laboring patient in good fluid and electrolyte balance, turning the patient to the lateral position, or progressive elevation of the legs as long as the patient is in the supine position, have been suggested previously.[7] It seems that the use of single intravenous doses of pressor agents alone will not bring about significant improvement in blood pressure levels of laboring patients.[8] Such improvement is more reliably obtained by alterations suggested above.

This study is in agreement with the findings of Noriega Guerra and colleagues[15] and at variance with those of Wingate and associates[21] who found that fetal heart rate patterns of late deceleration occurred in 33.3 per cent of patients receiving epidural anesthesia and that some of these abnormal fetal heart rate patterns were associated with maternal hypotension, while others were not. Our study revealed only one case of fetal tachycardia and late decelerations following moderate hypotension. The administration of oxygen to the mother and correction of the hypotension eliminated the early acidosis developing in that fetus. Furthermore, when maternal hypotension has been detected, application of standard measures might have prevented that undesirable fetal side effect so frequently found by those authors.[21]

This study suggests that the addition of epinephrine to the anesthetic solution triggers a diminution of uterine activity and not only does not give "cardiovascular support" to counterbalance the hemodynamic effects of sympathetic blockade but may dangerously worsen these effects.

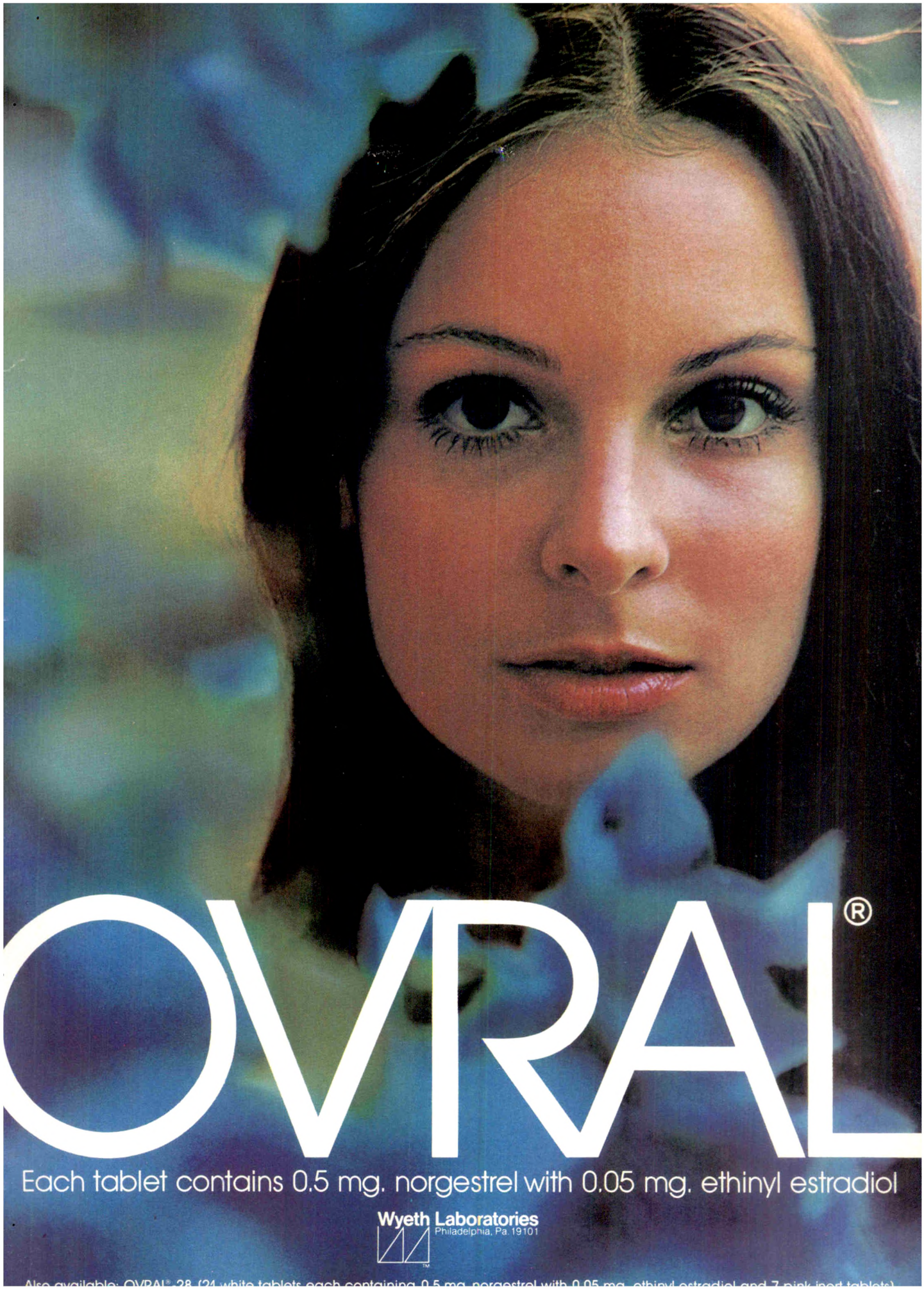
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Columbia University College of Physicians & Surgeons announces its annual postgraduate course entitled, "Review Course in Obstetrics and Gynecology," to be held at Columbia-Presbyterian Medical Center, Monday through Friday, October 25-29, 1976. Some of the speakers are Drs. R. Vande Wiele, R. Richart, R. Neuwirth, Associates, and guest lecturers. It will include a survey of the major clinical and pathologic problems pertaining to the female reproductive system. Emphasis will be on the diagnosis and management of obstetric and gynecologic disorders, including infertility, endocrine problems, and malignant diseases, with the use of modern advances in basic knowledge and clinical practice. There will be a review of gynecologic pathology. The course is divided as follows: gynecologic oncology, perinatal medicine, gynecology and obstetrics, reproduction control behavior, and endocrine disorders. The fee is $250 (residents $125). For registration, write to: Jose M. Ferrer, Jr., M.D., Associate Dean, 630 W. 168th St., New York, New York 10032. Telephone: (212) 694-3682.


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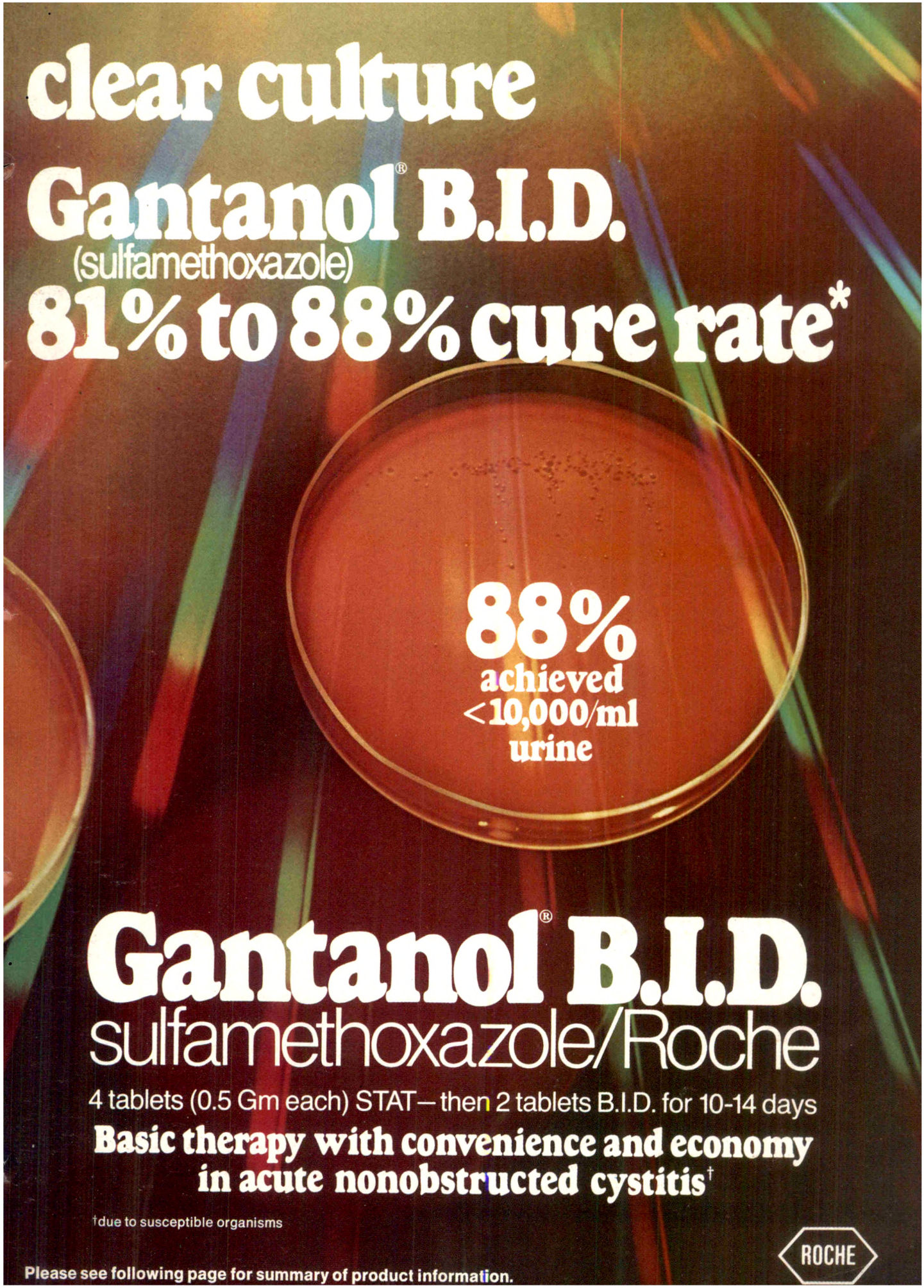
81%
achieved zero colony count/ml urine

83%
achieved <1000/ml urine

*In a new study 8 out of 10 patients with acute lower urinary tract infection, primarily cystitis, achieved sterile urine. All infections were nonobstructed. Susceptible organisms included *E. coli*, *Klebsiella-Aerobacter*, *Proteus mirabilis* and *Proteus vulgaris*.

No. of patients	Sterile urine	Clear culture <1000 organisms/ml urine	Clear culture <10,000 organisms/ml urine
406	81% (330)	83% (339)	88% (357)

Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey

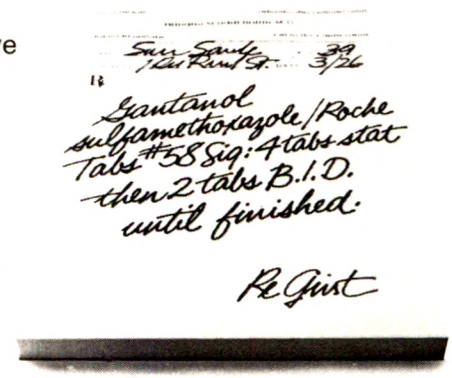

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in acute nonobstructed cystitis†
†due to susceptible organisms
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Please see following page for summary of product information.

Gantanol® B.I.D.
sulfamethoxazole/Roche

Basic therapy with convenience and economy in acute nonobstructed cystitis*

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- Effective in nonobstructed cystitis.
- Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- Convenient, economical B.I.D. dosage.
- Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.



*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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Brief Summary

Indications: For replacement therapy of estrogen deficiency associated with the menopausal syndrome, female hypogonadism (hypogenitalism), amenorrhea, female castration, or primary ovarian failure; in the management of senile vaginitis, in kraurosis vulvae with or without pruritus; for the prevention of postpartum breast engorgement; in the management of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology; in inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: In known or suspected carcinoma of the breast (except in cases of progressive disease not amenable to surgery or irradiation, occurring in women at least five years postmenopausal or in men in whom castration is not feasible), in other known or suspected estrogen-dependent neoplasia, thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or in patients with a past history of these conditions, in markedly impaired liver function, and in cases of undiagnosed abnormal genital bleeding.

Warnings: The drug should be withdrawn immediately if there is any evidence of thrombophlebitis, cerebral vascular disorders, pulmonary embolism, retinal thrombosis, proptosis, diplopia, migraine, papilledema, or retinal vascular lesions. Estrogens may be excreted in the mother's milk; the long range effect on the infant has not yet been determined. Hypercalcemia may occur in 15% of breast cancer patients with metastases, indicating progression of bone metastases. If this occurs, estrogen administration should be stopped.

Maternal ingestion of diethylstilbestrol during pregnancy has been associated with the occurrence of vaginal carcinoma in the offspring. Whether this association is applicable to all estrogens is not yet known, but the use of any estrogen in pregnancy is not recommended.

Precautions: Some individuals may exhibit undesirable manifestations of excessive estrogenic stimulation. Estrogens should be used cautiously in patients with epilepsy, migraine, asthma, cardiac or renal disease, or a history of psychic depression. If unexplained or excessive vaginal bleeding occurs, the drug should be discontinued and a thorough investigation made to ascertain that a malignancy is not present.

Pre-existing uterine fibromyomata may increase in size, and patients should be periodically examined. A pre-treatment physical should include a Pap smear and special attention to breast and pelvic organs. These drugs should be used cautiously in women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms. Since continuous use of estrogens will result in prolonged stimulation of the endometrium and breast, estrogens should be administered cyclically.

Estrogens may cause a decrease in glucose tolerance so diabetic patients should be closely observed. These drugs influence the metabolism of calcium and phosphorus and should be used cautiously in patients with metabolic bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Treatment with estrogens may mask the onset of the climacteric. Because they effect epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is not complete.

Prolonged high doses will inhibit anterior pituitary functions, so the drug should be used cautiously in patients in whom fertility is desired.

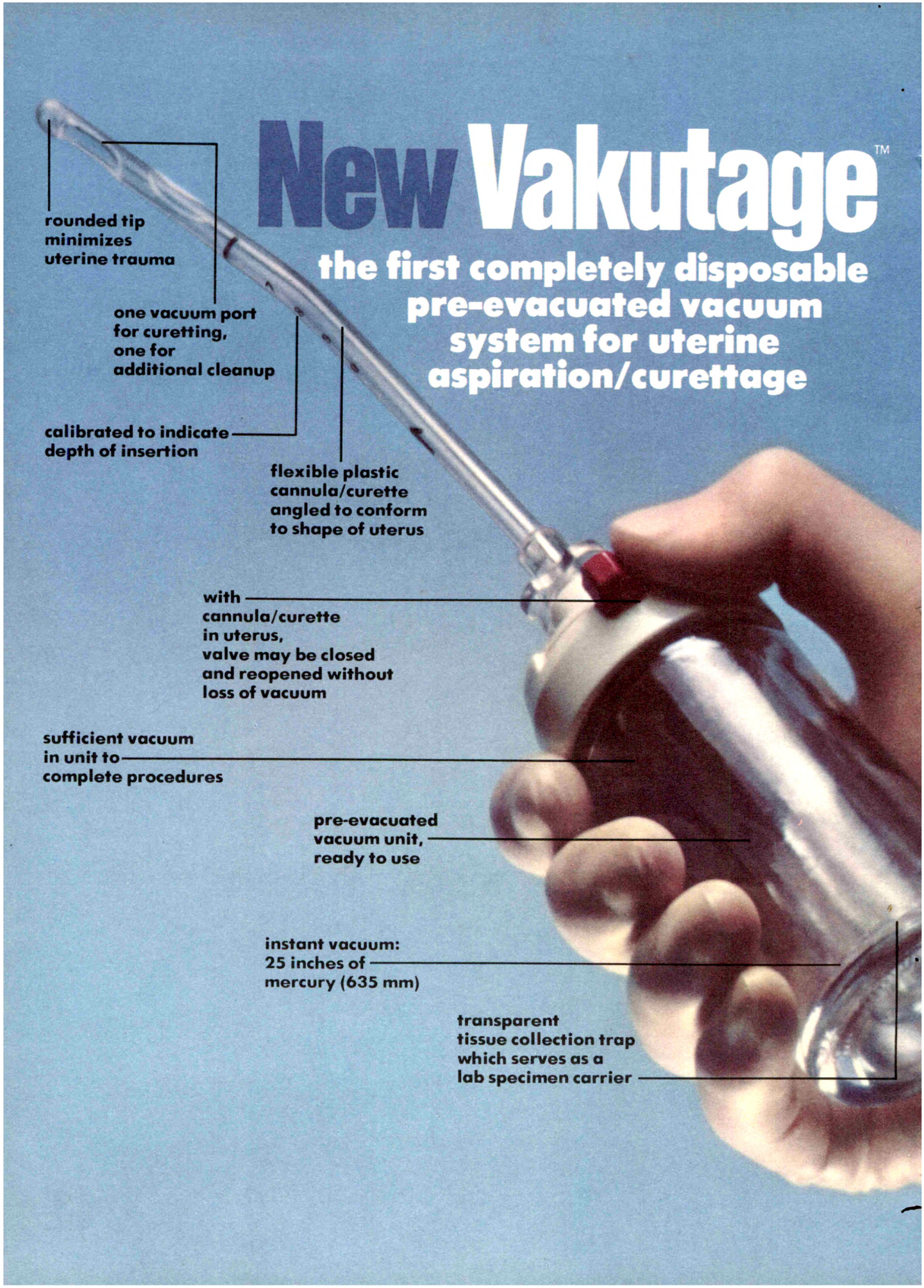
Urinary stress incontinence may occur in non-pregnant women with large doses. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Certain endocrine and liver function tests may be affected. If such tests are abnormal they should be repeated after the drug has been withheld for two months. Any possible effect of prolonged therapy on pituitary, ovarian, adrenal, hepatic, or uterine function will require further study.

Adverse Reactions: Adverse reactions to estrogen therapy may include: Gastrointestinal: nausea, anorexia, vomiting, abdominal cramps, bloating, cholestatic jaundice, and increase or decrease in body weight. Genitourinary: sodium and water retention, breakthrough bleeding, spotting, and withdrawal bleeding, increased cervical mucus, reactivation of endometriosis, and cystitis-like syndrome. Endocrine: breast swelling and tenderness, possible diminution of lactation when given immediately post partum, increased blood sugar levels, and decreased glucose tolerance. Central Nervous System: headaches, mental depression, increase or decrease of libido, nervousness, dizziness, fatigue, irritability and malaise. Dermatologic-Hypersensitivity: loss of scalp hair, allergic reactions and rashes, hemorrhagic eruption, itching, erythema nodosum, and erythema multiforme. Musculoskeletal: backache. Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches. Hematologic: A statistically significant association has been demonstrated between the use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence suggests an association, the relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuroocular lesions (e.g. retinal thrombosis and optic neuritis). Miscellaneous: Premenstrual-like syndrome and precipitation or aggravation or porphyria cutanea tarda in predisposed individuals.

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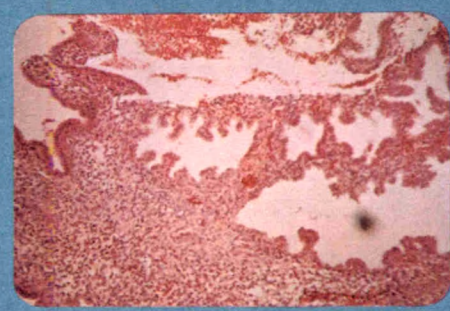
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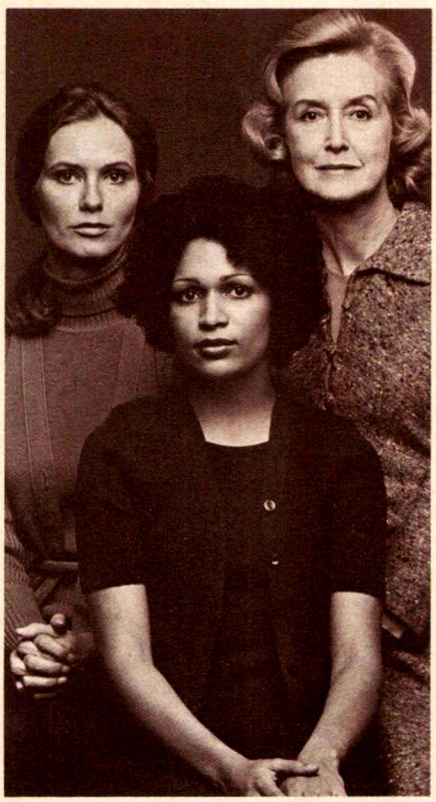
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* Data on file at Warner/Chilcott Medical Department.
† In rare instances of inadequate vacuum, the used collection unit can be replaced by another unused one, without removing cannula/curette from uterus.

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CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and 6 references. Illustrations or additional references require a proportionate reduction in total words.

Demonstration of gonadotropin during the second half of the cycle in women using intrauterine contraception

CARL G. BELING, M.D.
LARS L. CEDERQVIST, M.D.
FRITZ FUCHS, M.D.
New York, New York

A highly sensitive pregnancy test based upon partial purification of urinary gonadotropins by Sephadex gel filtration and concentration of the gonadotropin-containing fraction by lyophilization has been developed. Values over 100 I.U. per liter after Day 22 are considered to indicate conception. They are verified by radioimmunoassay (RIA) of the β-subunit of human chorionic gonadotropin (HCG) in plasma. Urine samples from users of intrauterine contraception were examined at random. Among samples collected after Day 21, 14 contained more than 100 I.U. per liter. In three of these cases, RIA of the β-subunit HCG in plasma was employed and verified the results. The results support the hypothesis that intrauterine contraception interferes with implantation and establishment of pregnancy but not with fertilization and blastocyst formation.

IN RECENT YEARS, many attempts have been made to improve the immunologic pregnancy tests. The aims have been to improve sensitivity as well as specificity. The highest degree of sensitivty has been achieved by radioreceptor assays,[1] while assays based upon antibodies against the β-subunit of human chorionic gonadotropin (HCG) have the highest level of specificity.[2] Sensitivity and specificity are both of essence for the study of the first postconceptional weeks, particularly to settle the question of whether the dividing ovum produces HCG before implantation, for which there is considerable evidence[3] but not full agreement.

Assays with a high degree of sensitivity, even if they do not distinguish between HCG and luteinizing hormone (LH), are useful because they permit the diagnosis of fertilization before the first missed period.

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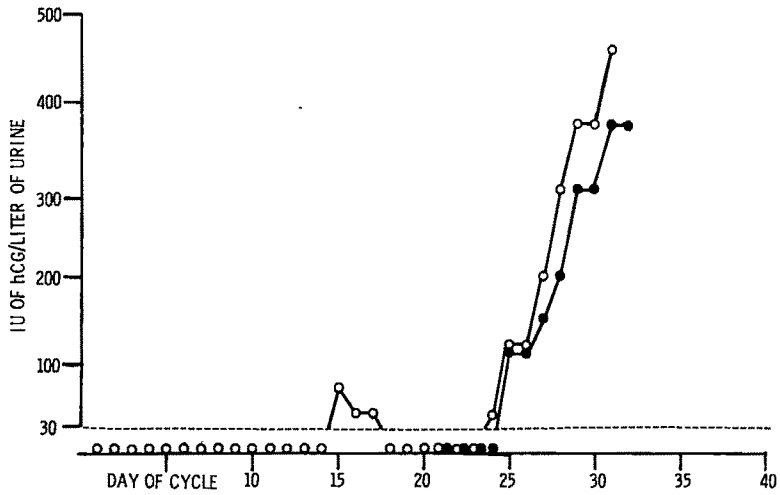


Fig. 1. Serial assays of urinary HCG/LH in two women who were followed from Days 1 and 21, respectively, during cycles in which fertilization occurred and normal pregnancies followed.

This can be of value in cases of induced ovulation, insemination, and the insufficient luteal phase syndrome.

We have used a sensitive urine assay to examine a group of patients using intrauterine contraception. When it was found that a surprisingly high percentage had a measurable level of gonadotropin in the second half of the cycle, the findings were confirmed by HCG β-subunit radioimmunoassay (RIA) in plasma.

Methods and material

The method used in the present study is based on purification of urinary gonadotropins by Sephadex gel filtration, lyophilization of the partially purified gonadotropin fraction, and determination of the gonadotropin content in the lyophilized material by a hemagglutination-inhibition test.* After filtration, 5 ml. of urine is applied to a glass column measuring 1 by 25 cm. and packed with 15 ml. or Sephadex G25 gel, which has been swelling in distilled water for 24 hours. The columns are then eluted with distilled water and collected in 24 separate 1 ml. fractions.

In urine samples collected during the third trimester of pregnancy (No. = 12), Fractions 7 through 11 contained 87 ± 4.5 per cent of the HCG. The ultraviolet-280 mμ absorbancy peak was found within these fractions.

In the present study all 24 volumes were not collected individually. Instead, 5 ml. of the sample was first applied to the column. Then 1 ml. of distilled water was added, which moved the gonadotropin front down to the bottom, centered glass plate of the column. The gonadotropin peak was then eluted with 5.5 ml. of distilled water and lyophilized. The lyophilized material was dissolved in 0.2 ml. of distilled water and centrifuged, after which 0.1 ml. of the sample was withdrawn with a pipet for the Pregnosticon test. Since this test measures the presence of 750 I.U. of HCG per liter of urine and our procedure results in a twenty-five–fold concentration, a positive result indicates the presence of at least 30 I.U. of HCG per liter of urine. Higher levels were determined by appropriate dilutions. In 280 urine samples from nonpregnant women, six false positive reactions were obtained.

For verification of the urinary findings, a radioreceptor assay for serum HCG/LH[1] and a HCG β-subunit RIA[2] were used. The method was first used to assay HCG/LH on a daily basis from Day 1 in one subject and from Day 21 in another, both of whom conceived and had uneventful pregnancies (Fig. 1). The sensitivity of the method permitted the demonstration of the urinary LH peak at the time of ovulation. A steep rise in gonadotropins was observed from Days 24 to 25, suggesting that pregnancy could be predicted the ninth to tenth postovulatory day.

Individual urine samples were initially collected from 101 women using intrauterine contraceptive devices (IUD's) at their regular visits to our Family Planning Clinic. Later, 30 additional women both were tested with the urine method and had blood samples analyzed with specific radioreceptor assays for HCG/LH[1] and the β-subunit HCG.[2] Subjects with proteinuria were excluded. The types of IUD's inserted in

*Pregnosticon, Organon, Inc., 375 Mt. Pleasant Ave., West Orange, New Jersey 07052.

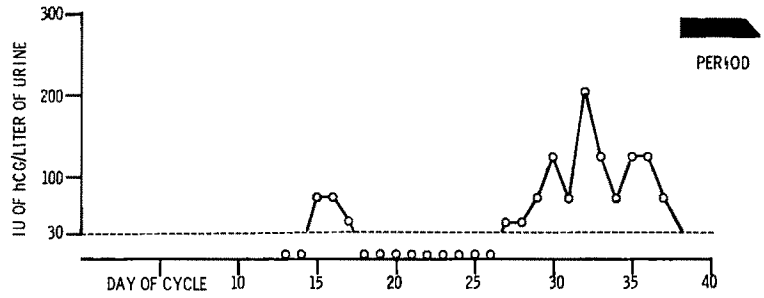


Fig. 2. Daily assays of urinary HCG/LH from Day 13 of the menstrual cycle in a 34-year-old woman who had had a Copper-T device in the uterus for two years. There were no clinical signs of pregnancy.

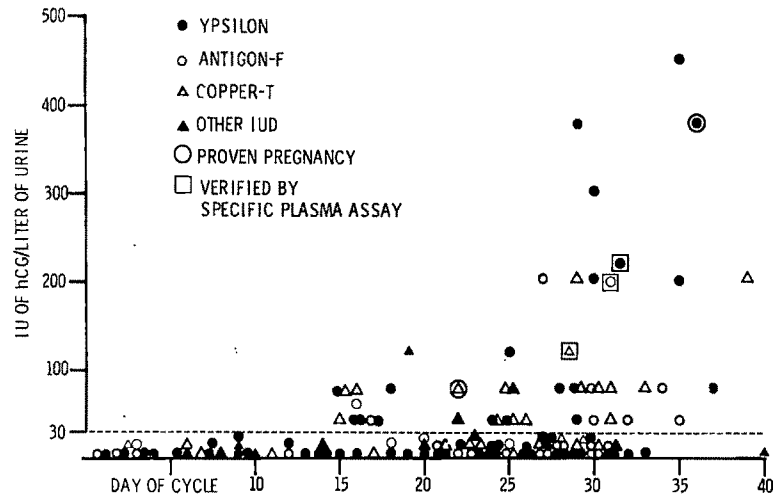


Fig. 3. Levels of HCG/LH in individual urine samples collected in 131 users of intrauterine contraception at regular visits. Values are plotted from the first day of the last menstrual period. The sensitivity of the assay (30 I.U. per milliliter) is indicated by a dotted line. Negative results have been grouped below this line.

our clinic were the Antigon-F, the Copper-T and the Ypsilon (small size).[5] In addition, women with other types of IUD's inserted elsewhere were examined.

Results

There was no measurable HCG/LH in the IUD users during the first 14 days of the menstrual cycle. However, there was a considerable incidence of measurable HCG/LH excretion on Days 15 to 18 and from Day 22 onward. Values elevated at midcycle most likely represent excretion of LH at the time of ovulation.

One patient with a Copper-T was followed with daily determinations of urinary HCG/LH from Day 13 (Fig. 2). She had slightly elevated values in midcycle and measurable levels of urinary gonadotropins in the late luteal phase. In contrast to the raise observed in pregnancy (Fig. 1), this second HCG/LH peak leveled off after a few days and did not exceed 300 I.U. per liter of urine.

The findings of positive values in 32 of 73 samples from the second half of the cycle was so surprising that we decided to collect both urine and blood samples from 30 additional subjects and determine whether the findings could be confirmed with a specific radioreceptor assay for HCG/LH[1] and HCG β-subunit RIA.[2] The results indicate that when the urinary levels exceed 100 I.U. per liter, the presence of HCG can be demonstrated in the plasma as well (Fig. 3).

Comment

The finding of measurable amounts of gonadotropin in the urine in the second half of the cycle in a substantial percentage of users of intrauterine con-

traception is of considerable interest. Even when values below 100 I.U. per liter are discounted as unspecific since no HCG could be demonstrated in the plasma at these levels, we still have 14 positive values in 92 subjects in the second half of the cycle, of which only two developed clinical signs of pregnancy. This indicates a very high conception rate in users of intrauterine contraception as compared to the incidence of clinically manifest pregnancy. For the Antigon-F and Copper-T, our pregnancy rates are around one per 100 woman-years, and for the Ypsilon (small size) the rates are somewhat higher.[5] Unfortunately, in the present pilot study, where samples were collected at random when the subjects appeared for regular examinations, the temporal relation to ovulation and subsequent menstruation is not known. All we have been able to ascertain at follow-up is that, with the exception of two, the patients did not develop clinical signs of pregnancy (Fig. 3).

It has long been suspected that a large percentage of conceptions are lost around the time of implantation.[6] The new, highly sensitive assays for HCG should permit a study of the true incidence of conception in unprotected, sexually active women and reveal the incidence of early or subclinical abortion. The finding of a high conception rate and a low pregnancy rate in users of intrauterine contraception is consistent with the hypothesis that the IUD does not prevent fertilization and blastocyst formation but interferes with implantation and the establishment of pregnancy. Almost identical results have been obtained by Landesman and associates* in a group of Copper-T users by means of radioreceptor assay for HCG/LH and RIA for the HCG β-subunit in plasma.

*Personal communication.

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Galactorrhea-amenorrhea: Psychological interaction with neuroendocrine function

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Further substantiation of the interaction between psychological disease and the onset of galactorrhea-amenorrhea is presented in women who underwent intensive psychometric and neuroendocrine evaluation prior to the use of the dopamine agonist 2-Br-α-ergocryptine (CB-154). Normalization of a previously distorted psychometric test profile in each woman was accompanied by a profound decline in prolactin and an unexpected alteration in the peripheral concentrations of norepinephrine and dopamine-β-hydroxylase. Cessation of galactorrhea and resumption of menses were observed in each instance.

MENSTRUAL IRREGULARITIES can be associated with psychological dysfunction, but the organic basis underlying this association remains unclear. In a recent report from this laboratory,[1] 13 women experienced galactorrhea-amenorrhea following oral contraceptive withdrawl (postpill galactorrhea-amenorrhea [PPGA]) and were thought to exhibit a psychogenic disturbance believed to be a factor in the etiology of the disorder. The symptomatology included altered prolactin (HPRL) secretion, absence of cyclic gonadotropin secretion, and galactorrhea.

Elevations in peripheral HPRL levels are known to occur following the application of noxious stimuli. Estrogenized rats placed under conditions of constant stress experienced inappropriate lactation, implying that a chronic alteration in prolactin secretion might be responsible.[2]

In a preliminary attempt to assess the role of stress in the etiology of PPGA, psychological evaluation of three women was made concurrent with the determination of peripheral HPRL concentrations. In addition, to evaluate sympathetic nervous discharge as an indicator of stress, peripheral catecholamines, including plasma levels of norepinephrine (NE) and the enzyme responsible for its synthesis, dopamine-β-hydroxylase (DBH), were measured. The objectives of the study were several: (1) to identify the presence of a psychogenic disturbance in women with PPGA, (2) to determine if this precipitated or was actually causally related to the onset of PPGA, and (3) to evaluate the effects of a dopamine agonist, 2-Br-α-ergocryptine (CB-154), on HPRL secretion, mental function, and peripheral NE and DBH concentrations.

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Material and methods

Three women between 25 and 30 years of age with persistent galactorrhea and amenorrhea for at least two years following withdrawal of oral contraceptives were studied. Thyroid function was normal as was polytomography of the sella turcica. Two of the women, Cases 1 and 2, agreed to receive CB-154,* 2.0 mg. orally three times a day for the first month, then 2.5 mg. orally three times a day thereafter, as treatment

*2-Brom-α-ergocryptine supplied by Sandoz Pharmaceuticals, Div. of Sandoz-Wander, Inc., Route 10, East Hanover, New Jersey 07936.

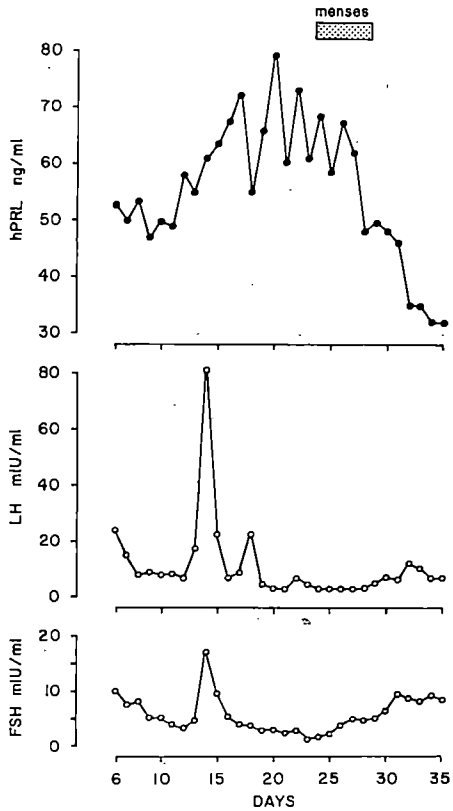


Fig. 1. Daily plasma levels of HPRL, LH, and FSH obtained from the patient who received only counseling. Blood sampling was begun six days after the counseling session.

for 12 weeks. A placebo was administered between Weeks eight and 10 of treatment to assess the effects of CB-154 withdrawal. In Case 3, the patient agreed to obtain psychiatric counseling as her only treatment. In Cases 1 and 2, the patients underwent in-depth historical and physical examination and psychometric testing prior to receiving medication and at eight, 10, and 12 weeks of treatment.

Blood samples, anticoagulated with acidified citrate-dextrose, were obtained via an antecubital vein with the patient in the supine position and with pulse and blood pressure stabilized. The samples were centrifuged in a refrigerated clinical centrifuge, and the resulting plasma fraction was then stored at −70° C. until assayed for HPRL, NE, and DBH. In Case 3, the patient received only counseling and underwent daily venipuncture for 30 days beginning six days following the initial session. An in-depth psychological interview was carried out after the completion of daily blood sampling. Radioimmunoassays for 0 plasma HPRL, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were performed by methodology previously reported.[1] Plasma NE levels were determined by the method of Henry and

Table I. Plasma HPRL, NE, and DBH prior to (Time 0) and following CB-154 administration. Placebo was given between Weeks eight and 10

Time (weeks)	*HPRL (ng./ml.)*	*NE (pg./ml.)*	*DBH (activity*)*
Case 1			
0	45	462	842
4†	10.5	193	847
8	8.6	151	939
10	74	141	712
12	12	74	757
Case 2			
0	61	260	979
4†	5.4	272	1,050
8	5.0	205	952
10	118	167	896
12	7.3	132	676

*Activity expressed in nanomoles of phenolethanolamine per milliliter per hour.

†Psychometric testing was not performed at four weeks of treatment.

associates[3] while DBH determinations were performed with a modification of the method of Weinshilboum and Axelrod.[4] Patients were evaluated psychometrically with two self-report techniques (Minnesota Multiphasic Personality Inventory [MMPI] and Symptom Distress Check List [SCL-90]) and two fantasy techniques (Thematic Apperception Test [TAT] and Rorschach).

Results

Table I presents the values of HPRL, NE, and DBH obtained in the two women receiving CB-154. Noticeable declines occurred in HPRL and NE levels during treatment, followed by a clear rebound in plasma HPRL during two weeks of placebo therapy. Menses resumed between four and five weeks after the initiation of CB-154 therapy but did not recur until the tenth week of treatment in Case 2.

In Case 3, the patient experienced a decline in plasma HPRL concentration following the mere application of psychiatric counseling. Menses returned promptly within 30 days after an absence of almost three years and were preceded by a surge in LH and FSH within 30 days of the first counseling session, as shown in Fig. 1. Galactorrhea ceased completely by the time of the first menstrual period.

From interviews and psychometric test results, each woman exhibited evidence of multiple and severe chronic and acute stress reactions as shown below.

Case reports

Case 1. A 27-year-old black woman developed galactorrhea-amenorrhea following oral contraceptive administration given subsequent to the term delivery of

Table IIA. T-score values on MMPI scales for Cases 1 and 2*

Scale	*Pretest*	*8 Weeks*	*10 Weeks*	*12 Weeks*
Case 1				
Scale 2 (depression)	80	61	64	63
Scale 9 (hypomania)	60	81	78	70
Mean of all 10 clinical scales	69	64	59	53
Case 2				
Validity K Scale (defensiveness)	50	64	69	69
Scale 2 (depression)	65	51	47	57
Scale 3 (hysteria)	73	72	65	67
Mean of all 10 clinical scales	56	52	51	54

*Mean for the general population is 50, with S.D. of 10. The higher the score, the worse the psychopathology.

Table IIB. T-score values on the SCL-90 scales for Cases 1 and 2*

Scale	*Pretest*	*8 Weeks*	*10 Weeks*	*12 Weeks*
Case 1				
Depression	56	42	32	26
Anxiety	54	43	35	31
Mean distress level (9 scales)	53	33	38	29
Case 2				
Depression	40	31	28	31
Anxiety	48	37	25	32
Mean distress level (9 scales)	36	29	29	29

*Mean for psychiatric outpatients is 50, with S.D. of 10. The higher the score, the more severe the symptoms.

a stillborn female infant. Her early family history revealed stresses related to the divorce of her parents and the remarriage of her mother by the time the patient was seven years of age. At the time of the initial interview and testing, she was acutely and psychotically depressed about her stillborn child (Tables IIA and IIB) with a pathologic preoccupation of thoughts about the reproductive system (80 per cent of Rorschach responses).

After placement on CB-154 and without knowledge of the test results or the extent of the psychiatric disease, the patient showed a substantial amelioration of both mood and symptoms, more so after experiencing the first menstrual period in over 25 months. At 12 weeks of treatment, she did not give any psychopathologic responses and was virtually asymptomatic (all scales on the MMPI and SCL-90 were within normal limits).

Case 2. This patient was a 27-year-old white woman who experienced irregular menses since menarche. While numerous trials with a variety of oral contraceptive preparations regulated the menstrual cycle, galactorrhea and amenorrhea soon developed. The earliest memories of anxiety were related to overhearing violent arguments between her mother and her alcoholic father. At the time of the initial interview and testing, the patient appeared depressed and anxious (Tables IIA and IIB). Her responses were guarded on the TAT while the Rorschach revealed substantial underlying tension and problems with regard to family members.

After eight weeks of CB-154 therapy, the patient improved symptomatically although she was more defensive about her family life.

Case 3. This 25-year-old white woman had experienced symptoms of amenorrhea and galactorrhea for 23 months before consultation. Following menarche, she had regular cycles until entering college when she experienced irregular menses. She was treated with oral contraceptives, but withdrawal led to the PPGA symptomatology.

In childhood, this patient had difficulties in establishing a satisfactory father-daughter relationship. This problem was made more complex as the patient's father suffered a myocardial infarction each time he disciplined the patient on four separate occasions. After her marriage, the patient moved away from home against the wishes of her father while simultaneously encountering pressures from her newly obtained job.

In the counseling session, the patient ventilated her dissatisfaction about her ability to cope with pressures from work, home, and family. She was encouraged and supported in her decision to quit her demanding

full-time job and to pull herself away from close family dependency and guilt. Menses spontaneously returned (see Fig. 1) and have been regular since.

Comment

The psychological test results seem to support the thesis that an underlying, easily demonstrable psychological disturbance is present in women with PPGA. Furthermore, in Case 3, an awareness of the causes of this psychologic disturbance and a willingness to try other ways of coping with stress apparently led to the resumption of cyclic gonadotropin secretion. This case also illustrates that correction of the psychological condition preceded resumption of cyclic gonadotropin secretion, implying that the presence of galactorrhea-amenorrhea may not have contributed to development of an abnormal psychological state.

While peripheral levels of HPRL are known to increase in response to a variety of stimuli including stress, no adequate explanation can be given as yet for the neurochemical dynamics which control HPRL secretion in such circumstances. Catecholamine regulation of HPRL and gonadotropin secretion has received much attention in animals. Opinions vary as to the regulatory role of catecholamines directly on pituitary function or an intermediary role inasmuch as they stimulate the secretion of pituitary stimulating or inhibiting factors from hypothalamic nuclei.[5] Conceivably, alterations in catecholamine-dependent neurotransmission could result in a disturbance of cyclic gonadotropin secretion and an eventual absence of such secretion accompanied by increased HPRL secretion similar to what has been observed in women with PPGA. Chronic disruption of the normal pathways of neurotransmission might be produced by multiple severe stressful stimuli.

Oral contraceptives and, indeed, pregnancy by reason of a hormonal influence on cerebral function may actually precipitate the onset of PPGA in susceptible women. It is the biological and psychological susceptibility of these women that is currently under investigation.

The administration of CB-154 causes a rapid decline in peripheral proclactin levels, presumably by preventing its release at the level of the pituitary gland.[6] The results of this study show that drug therapy was associated with a gradual decline in peripheral NE levels with a simultaneous, possibly coincidental, normalization of reported mood and symptoms. Alterations in mood in patients receiving CB-154 have been noted by other investigators, but psychological testing was not performed.

While CB-154 administration may temporarily modify the symptomatology of PPGA, elevated HPRL levels beyond the range of normal followed withdrawal of the medication between Weeks eight and 10 as shown in Table I. This elevation was not associated with any acute change in personality and mood, thus establishing that hyperprolactinemia did not have any acute effects on psychological function.

The basic personality of the patient treated with CB-154 was not apparently altered by the medication. Thus, the underlying psychological disturbance may remain in women with PPGA, further altering neuroendocrine regulation and accounting for the failure of these women and others to maintain cyclic gonadotropin secretion while no longer receiving CB-154. If altered psychodynamics are significant in the etiology of this condition, resulting in neurotransmission changes sufficient to promote hyperprolactinemia and absence of cyclic gonadotropin release, then a failure to correct the psychological dysfunction may lead to continued, excessive prolactin secretion and ultimately a demonstrable pituitary adenoma.

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Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Roentgen visualization of the placenta

WILLIAM SNOW AND CLILIAN BETHANY POWELL
American Journal of Roentgenology and Radiation Therapy, vol. 31, pp. 37-40, 1934

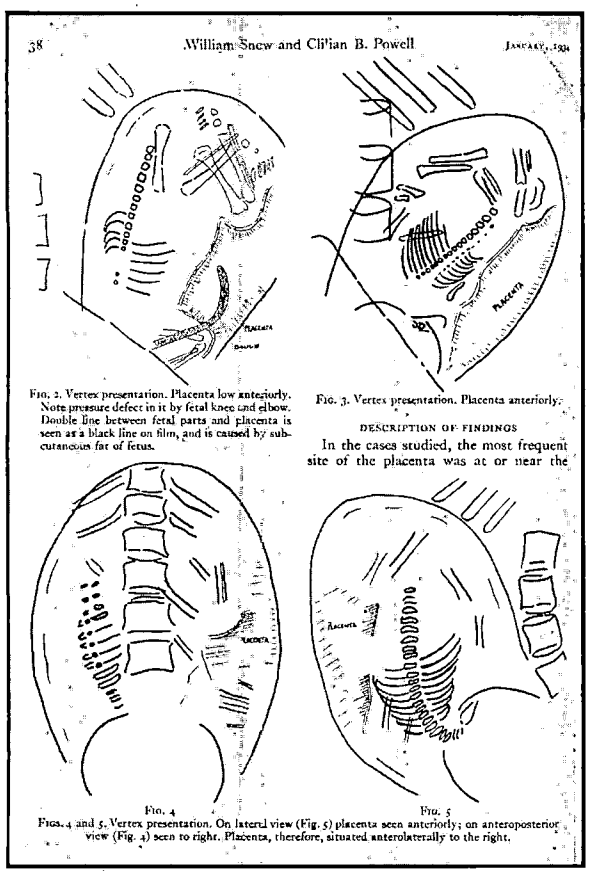

38 William Snow and Clilian B. Powell JANUARY, 1934

Fig. 2. Vertex presentation. Placenta low anteriorly. Note pressure defect in it by fetal knee and elbow. Double line between fetal parts and placenta is seen as a black line on film, and is caused by subcutaneous fat of fetus.

Fig. 3. Vertex presentation. Placenta anteriorly.

DESCRIPTION OF FINDINGS

In the cases studied, the most frequent site of the placenta was at or near the

Fig. 4

Fig. 5

Figs. 4 and 5. Vertex presentation. On lateral view (Fig. 5) placenta seen anteriorly; on anteroposterior view (Fig. 4) seen to right. Placenta, therefore, situated anterolaterally to the right.

Snow and Powell presented the first report of placentography. The authors observed, "We have been able to demonstrate the placenta in the routine roentgen examination of the abdomen of pregnant women in a very high percentage of cases . . . the most frequent site of the placenta was at or near the fundus. A much smaller proportion was lower down. . . . In practically all cases, the ventral part of the fetus faces it." Snow and Powell also described the dark line of demarcation between the fetus and surrounding soft structures and assumed that it was produced by the fetal subcutaneous tissue. The authors reported that the placental location was verified at cesarean section in several patients. They also described three cases of abruptio placentae. They concluded, "If, in the future, the procedure of injecting some radiopaque substance into the uterine cavity for diagnosis becomes definitely established, it will be logical to make a preliminary roentgen examination." In the following issue of the same journal, Ude, Weum, and Urner first described the diagnosis of placenta previa by placentography (Am. J. Roentgenol. Radium Ther. 31: 230, 1934).

COMMUNICATIONS IN BRIEF

This section is suitable for reporting cases, results of therapeutic trials, and descriptions of new procedures or instruments. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Maternal estrogen levels in two pregnancies complicated by severe fetal growth retardation with congenital anomaly

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IT IS WELL established that the estriol excreted in maternal urine is biosynthesized by the placenta from androgenic precursors formed by the fetal adrenals in pregnancy in the human subject. There is now widespread use of the maternal urinary estriol assay to assess fetal status and, in particular, fetal growth as pregnancy progresses; not surprisingly, low levels of estriol have been reported in association with intrauterine fetal malnutrition.

We wish to report on estrogen findings in the following two cases of severe fetal growth retardation with congenital anomaly.

N. C., a 26-year-old primigravida, had fetal malnutrition first suspected at 26 weeks of gestation. She was maintained on a high-protein diet and was given isoxsuprine (30 mg. four times a day) as a precautionary measure. Nevertheless, radiology and repeated ultrasound cephalometry from 33 weeks on indicated that the fetal size was two to three standard deviations below normal for the gestational age. Amniotic fluid obtained by amniocentesis at 38 weeks was yellow and abundant with 90 per cent fat cells and creatinine content of 1.6 mg. per cent. However, two weeks later, amniocentesis yielded scant and thick meconium-stained fluid, and pregnancy was terminated by cesarean section. The baby, in a breech position, weighed 1,250 grams, and the placenta weighed 350 grams (with cord and membranes). In addition to severe malnutrition, the infant presented at birth with musculoskeletal deformities involving the feet, hips, neck, and back. The head was disproportionately large with features of oxycephaly and low-set ears. During life, she had difficulty in swallowing, rectal prolapse, and abnormalities in the right hemidiaphragm with herniation of the right hepatic lobe into the right chest; death occurred at 27 days of age. Autopsy revealed the presence of a single horseshoe-shaped kidney (14.2 grams), marked pituitary congestion, adrenals of reduced size (total of 2.3 grams), and abnormalities in the lung (focal areas of atelectasis in both lower lobes), diaphragm (resulting in compression of the liver), and colon (malrotation with location of the cecum in the left lower quadrant). A "D" chromosomal abnormality ("marker" chromosome) identified during life was a familial variant (present in the father) and probably did not represent anything pathologic.

G. B., a 19-year-old primigravida, had a history of 40 weeks of amenorrhea following the use of contraceptive pills for one month. She was admitted for evaluation at 38 weeks after a diagnosis of probable intrauterine fetal death was made during antenatal follow-up elsewhere. Ultrasonic cephalometry revealed a severely growth retarded and possibly malformed but still viable fetus (there was definite cardiac activity) and also marked oligohydramnios. The mother was discharged at 39½ weeks when the fetal heart was still heard but three days later was delivered of a 1,050 gram stillborn macerated male fetus after spontaneous labor. The placenta weighed 280 grams. The head was disproportionately large. At autopsy (66 hours later) organ weights were found to be compatible with a 25 to 27 week pregnancy, and the adrenals were atrophic (total weight was 1 gram). All organs were in a state of autolysis. The only identifiable malformation was that of two horseshoe-shaped kidneys (total of 20 grams).

The maternal urinary and plasma estriol and plasma estradiol levels are shown in Fig. 1. The estradiol values best reflected the fetoplacental condition in both cases. The failure of urinary estriol values to do so, particu-

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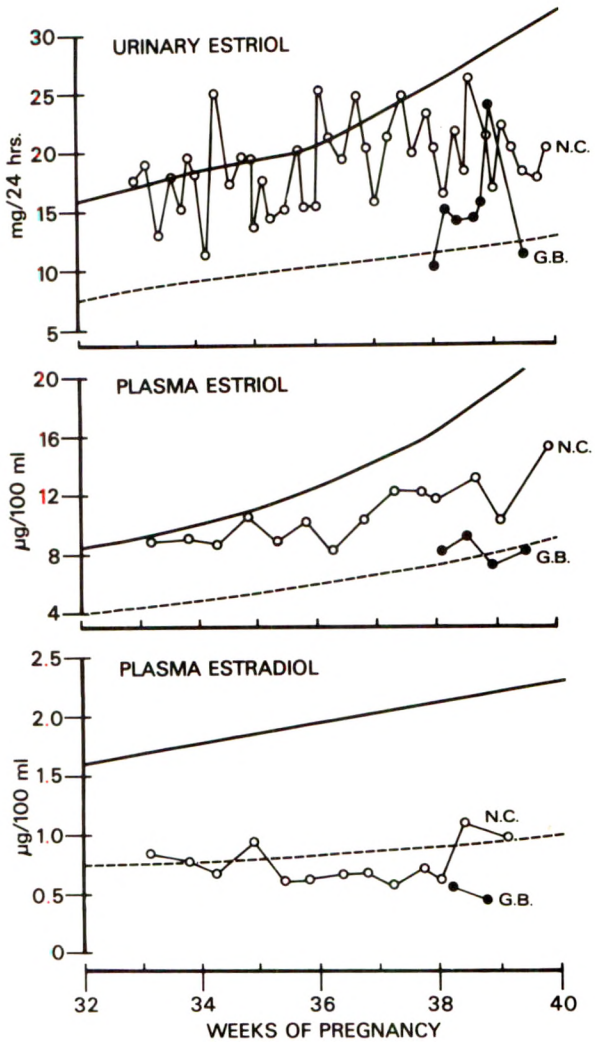


Fig. 1. Maternal estrogen levels in two pregnancies complicated by severe fetal growth retardation with congenital anomaly. The solid lines indicate the average values, and the dotted lines are the lower limits of values for normal pregnancies.

larly in Patient N. C., is intriguing: this finding is similar to that observed by Beischer and associates[1] in fetal growth retardation complicated by Potter's syndrome.

Although the infant of Patient N. C. had many features of Potter's syndrome, it remains undiagnosed with the possibility that this is an as yet unrecognized genetic syndrome. Apart from the growth retardation, the other apparent fetal abnormalities in common with the infant of Patient G. B. were the renal malformation and relatively small adrenals. There was also marked oligohydramnios in both cases at term; this could account for a number of the abnormalities observed in the infant of N. C.

We have previously observed low estradiol levels in uncomplicated fetal malnutrition,[2] and the present findings suggest that this endocrine parameter may better reflect fetoplacental function than do the estriol values when growth retardation is complicated by certain congenital anomalies, including those involving the fetal kidney.

In any case, whether the fetal malnutrition is complicated or not, it is open to question whether the maternal plasma estradiol levels reflect primarily the reduced placental size and the concomitant fetal growth retardation only secondarily.

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Lateral communicating double uterus with unilateral vaginal obstruction

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A VERTICAL vaginal septum is basically asymptomatic with regard to menstruation, unless the septum develops in such a way that one or both sides of the two hemivaginas are obstructed. In this latter circumstance, the accumulation of menstrual blood in the obstructed side or sides causes progressive dysmenorrhea until surgical correction brings relief. With obstruction of one side of the vagina, but with a lateral communication between the two halves of a double uterus above the level of the external ora, there exists a special situation which often is clinically puzzling and threatens future reproduction if not recognized and timely treated.

Relatively few cases of this special situation have been

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Table I. Reported cases of lateral communicating double uterus with unilateral vaginal obstruction

Reference	*Year*	*Age at first symptom*	*Age at definitive therapy*	*Treatment of anomaly*	*Fertility*		*Size of vaginal obstruction*	*Urological investigation*
					Prior to Treatment	*Subsequent treatment*		
Carrington[1]	1933	17	18	Hysterectomy, subtotal excision of septum	0	Dest.	L	N.A.
Woolf and Allen[2]	1953	10	20	Excision of septum	0	+	L	Ipsilateral renal agenesis
Trevoux[3]	1964	?	?	Hemihysterectomy—subtotal, excision of septum	?	?	R	Ipsilateral renal agenesis
Johansen[4]	1972	20	20+ "Some months"	Laparotomy, excision of septum	0	1	R	N.A.
Johansen	1972	13	13	Laparotomy, excision of septum	0	+	R	N.A.
Toaff[5]	1974	24	37	Hysterectomy—total, excision of septum	1(Term)	Dest.	R	Ipsilateral renal agenesis
Toaff	1974	14	38	Laparotomy, excision of septum	0	+	R	Ipsilateral renal agenesis
Toaff	1974	12	32	Laparotomy	2(Term)	+	L	Ipsilateral renal Agenesis
Toaff	1974	13(?)	22	Laparoscopy, excision of septum	0	+	R	Ipsilateral renal agenesis
Present series	1975	20(?)	24	Cesarean section, hemihysterectomy—subtotal, excision of vaginal septum	1(Term)	+	R	Ipsilateral renal agenesis
Present series	1975	12	13	Excision of septum	0	+	R	Ipsilateral renal agenesis

Dest. = Destroyed; + = fertility preserved; N.A. = information not available, R = rudimentary.

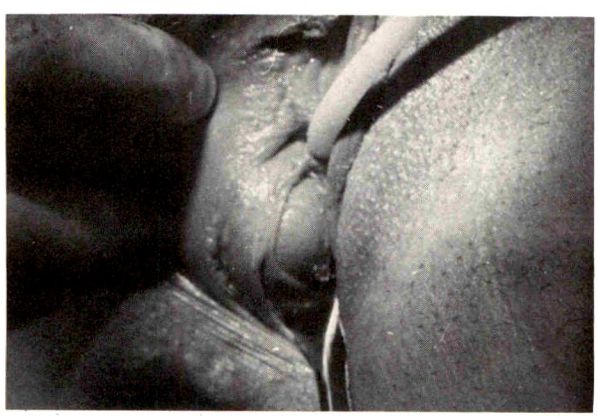


Fig. 1. Hematocolpos of the right vagina.

reported as such, but several examples have been included in general series on uterine and vaginal anomalies. Because of the threat to reproduction implicit in failure to recognize and promptly treat this anomaly, it is thought that it might be worthwhile to draw attention again to it by the report of two additional cases. With these cases, there seem to be 11 reported examples (Table I), although it is quite possible that there are other unidentified cases included in large general series of uterine and vaginal anomalies.

T. M. A. C. (Case 1) was first seen in May, 1973, because of secondary infertility. She was 24 years of age. During the first pregnancy, she noticed that the growth of the uterus was not symmetrical. Only the left side seemed to be enlarging. She went into spontaneous labor at term with active uterine contractions. After a prolonged labor, a cesarean section was done, and a bicornuate uterus was found. The baby died some hours after delivery, apparently as a result of the prolonged labor.

Up to the present time, she has been unsuccessful in becoming pregnant.

The menstrual cycles have been between 28 and 35 days with normal flow and no dysmenorrhea.

The basal body temperature curves were suggestive of

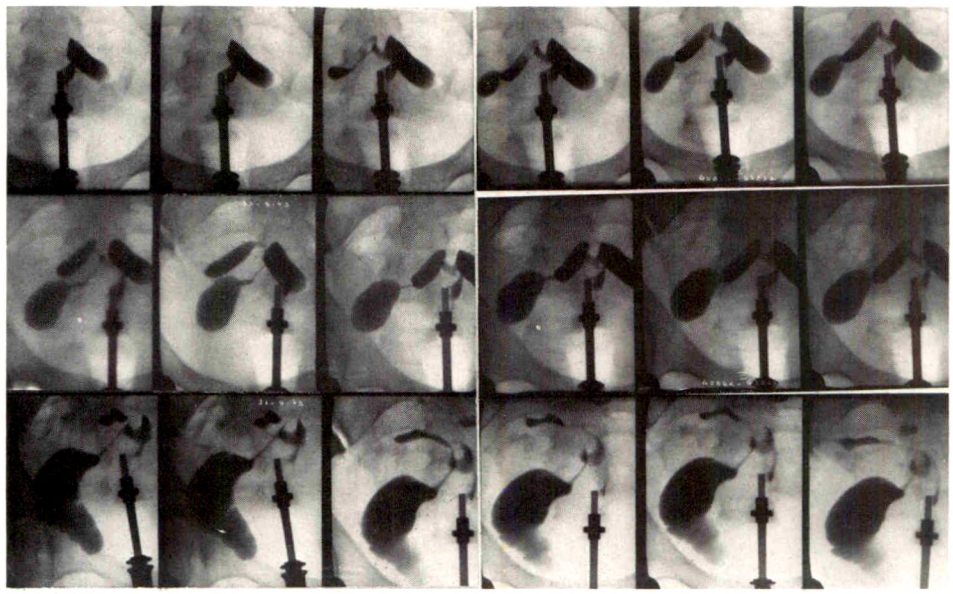


Fig. 2. Hysterograms showing the several stages of filling of the left uterus, right uterus, and right vagina.

ovulatory cycles. On vaginal examination in the fifth day of a cycle, a slitlike normal cervix was visualized; the external os had the shape of a vertical slit through which a chocolate-colored viscous discharge was flowing. The right wall of the vagina was bulging (Fig. 1). On pelvic bimanual examination, the right vaginal wall gave a cystic sensation. The corpus of the uterus was slightly enlarged, and in the fundus an anteroposterior depression could be felt. The adnexa were not palpable.

In view of these findings, a clinical diagnosis was made of a double communicating uterus with hematocolpos of a right occluded vagina.

An intravenous pyelogram showed agenesis of the right kidney. Hysterograms (Fig. 2) confirmed the diagnosis.

At laparotomy, a subtotal hemihysterectomy on the right side (Fig. 3) was performed. The right tube was saved and stitched to the left hemiuterus without attempting implantation.

The right vagina was incised and drained from below with a profuse flow of retained blood mixed with a purulent discharge. Cultures were taken, and *E. coli* were identified. Two months later, the right vagina and cervix appeared normal. The external os of the right cervix was similar to the one of the left side, i.e., a vertical slit. The vaginal mucosa had an entirely normal appearance, and a smear showed normal superficial cornified cells with pyknotic nuclei.

A hysterogram taken through the left cervix showed good patency of the left tube.

E. C. (Case 2) was born September 23, 1959. Pubertal development was normal, and she had menarche at age 11. The menstrual periods were always accompanied by some discomfort, which became progressively worse, until it was finally necessary for her to see a gynecologist, at age 12, because of the dysmenorrhea.

Vaginal examination disclosed an elongated cystic mass running along the entire length of the right vaginal wall. The cervix was small, and an elongated suprapubic mass appeared to be connected with the cervix.

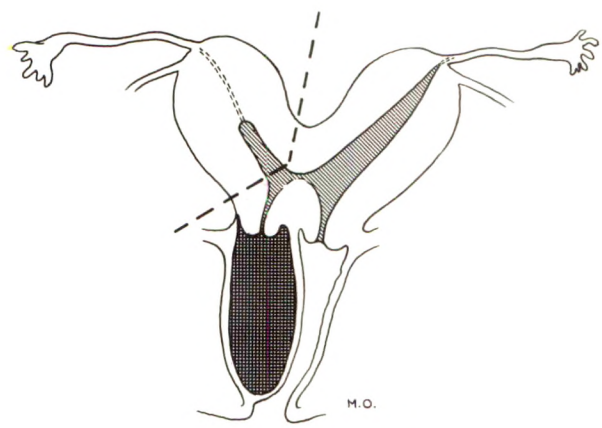


Fig. 3. A schematic representation of the genital tract as seen from the front. The right vagina is occluded and is filled with chocolate-colored fluid. The dotted lines represent the incision for the removal of the right uterus.

An intravenous pyelogram failed to reveal the right kidney, and cystoscopy showed the absence of a right ureteral orifice. With a panendoscope, a small opening in the cervical canal at about 9 o'clock was noted; into this opening, a small polyethylene tube was introduced through which radiopaque material was injected which made visible a small tubular structure deviating to the right. A hysterosalpingogram failed to reveal this intracervical opening but did show what seemed to be a unicornuate uterus on the left; the Fallopian tube was not visualized.

The patient seemed somewhat better after these preliminary examinations but, by September, 1972, she had developed leukorrhea which became very foul smelling and profuse.

These complaints required further investigation in July, 1973. Repeat hysterography showed what seemed to be a left



Fig. 4. Hysterogram taken through the left cervix showing what seems to be a unicornuate uterus with a single tube and spill of the radiopaque material into the peritoneal cavity.

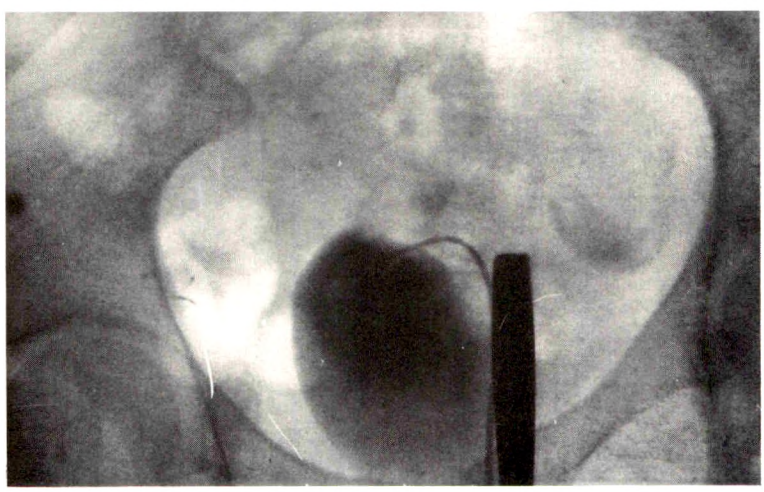


Fig. 5. An x-ray showing filling of the obstructed vagina after the introduction of a small ureteral catheter by means of a panendoscope through the small communication between the right and left side of the uterus.

unicornuate uterus with a delicate Fallopian tube and peritoneal spill (Fig. 4). By means of a panendoscope, a No. 7 whistle-tip ureteral catheter could be inserted in the small opening at 9 o'clock in the endocervical canal, and it then became apparent that the vaginal cystic mass could be filled and evacuated through the ureteral catheter. An x-ray disclosed what seemed to be an obstructed right vagina, but a right uterus or Fallopian tube was not seen (Fig. 5).

The diagnosis was made of a blind right vagina with transverse communication through the cervix between the two sides of a complete bicornuate uterus. An examination with the patient anesthetized and the vagina evacuated disclosed what seemed to be a right unicornuate uterus which had not been seen on the x-ray.

On July 6, 1973, with a ureteral catheter placed into the right vagina and the blind right vagina filled with 100 c.c. of saline, the septum was incised. This revealed the right vagina with a small atrophic cervix at the apex. The vaginal septum was excised.

Pathologic examination of the septum revealed normal squamous epithelium on the left (unobstructed) side, but, on the right side of the septum, columnar epithelium was present (Fig. 6). The gross appearance of the obstructed vagina suggested that the entire obstructed right vagina was lined with columnar epithelium, and a biopsy from the right fornix confirmed this.

Subsequent to operation, the patient's dysmenorrhea disappeared completely.

On examination, in July, 1974, one year after the removal of the septum, the endocervical epithelium, which had lined the blind right vagina, was being replaced by squamous epithelium, and hysterography taken through the right cervix revealed the left horn of the complete bicornuate uterus on the right with a delicate tube and spill.

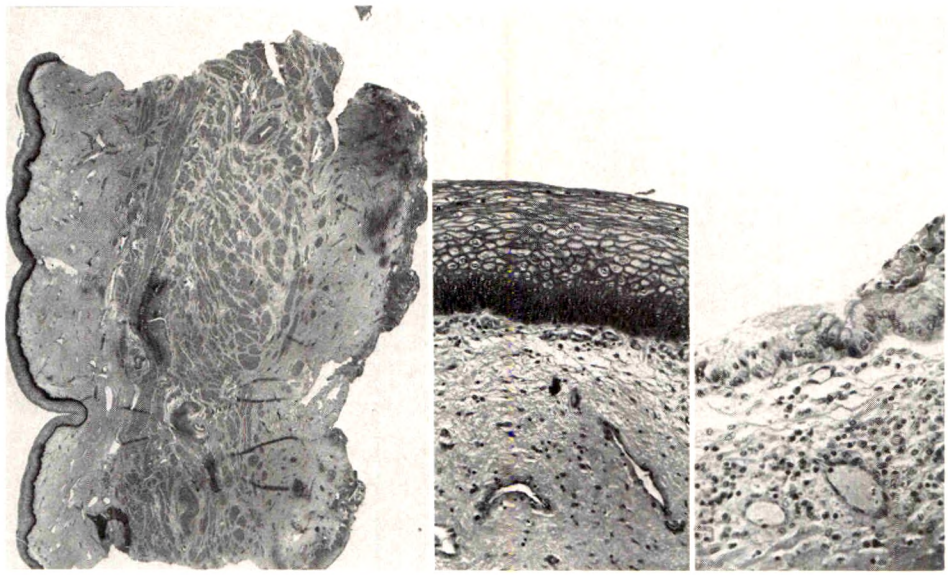


Fig. 6. Left: Low-power photomicrograph of the septum showing squamous epithelium on the side of the septum which lined the unobstructed vagina and columnar epithelium on the opposite side of the septum which lined the obstructed vagina. Center: High-power view of the squamous epithelium. Right: High-power view of the columnar epithelium.

The diagnosis was vertical vaginal septum with obstruction of the right vagina and a complete bicornuate uterus with lateral communication between the two endocervices.

In a series of 16 collected examples of "communicating uteri" to which he added four, Toaff[5] cited nine examples of unilaterally obstructed vaginas with a lateral communication between the two sides of a double uterus above the level of the external ora. As may be seen from the data of Table I and from the details in the original sources, this anomaly has several distinctive clinical features.

1. The anomaly has not been easily recognized. For example, in at least one reported case, the problem was not suspected until, at the time of total hysterectomy, two vaginas were discovered. However, the history of a vaginal mass of changeable size which, on occasion, might seem to disappear and/or a malodorous vaginal discharge often beginning after instrumentation of the cervix and distinctive radiographic features make the diagnosis relatively easy, if the nature of the anomaly is realized and considered as a diagnostic possibility.

2. As mentioned, instrumentation for diagnostic purposes is apt to induce infection in the obstructed side, so that surgical correction should follow reasonably promptly after the diagnostic studies.

3. Although laparotomy was performed in nine of the 11 collected cases, in most but not all instances, the laparotomy was undertaken in ignorance of the condition and turned out to be useful only for diagnostic purposes. In most cases, laparotomy is not necessary for diagnosis or therapy.

4. In all recorded examples of this anomaly, renal agenesis has been noted on the side of the obstructed hemivagina.

In addition to the above clinical features, the finding that the obstructed hemivagina in E. C. was lined with columnar epithelium is of interest with respect to the embryogenesis of the vagina. The basic observation that columnar epithelium is commonly found cephalad to a point of total failure of communication between what is presumed to be the junction of the epithelium of the down-growing Müllerian tubercle and the up-growing urogenital sinus was made as long ago as 1912, by Bell.[6] Kanagasuntharan and Dassanayakae,[7] who also studied this problem, pointed out that if the obstruction was not complete, i.e., there was even a small communication between the Müllerian duct and the urogenital vagina below the level of the squamocolumnar junction in the cervix, the squamous epithelium was then found above the obstruction and below the normally placed squamocolumnar junction in the cervix. Most likely, in the situation of incomplete obstruction, the original columnar epithelium of Müllerian origin has been secondarily replaced by squamous epithelium, presumably by metaplasia or epidermidalization. This view is supported by the course of events in E. C. where the columnar epithelium of the obstructed hemivagina was slowly replaced by squamous epithelium after removal of the obstructing vaginal septum.

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Papillary serous cystadenoma arising in a paramesonephric cyst of the parovarium

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NON-NEOPLASTIC CYSTS often arise in mesonephric and paramesonephric rests of the broad ligament, but true papillary tumors constitute a rare secondary complication of these cysts, especially of the paramesonephric cysts, as stressed by Janovski and Bozzetti[1] in their report of a papillary serous cystadenoma arising in a paramesonephric cyst of the mesosalpinx. Gardner and associates,[2] in their review of tumors of the broad ligament, listed nine serous cystadenomas without elaborating on their location, histogenesis, or histologic features. One of their cases, illustrated as fibropapillary serous cystadenoma, closely resembles both the case reported by Janovski and Bozzetti and the case presented here.

A 22-year-old nulliparous woman presented with intermittent pelvic pain unrelated to the menses. A cystic mass was felt in the left adnexa, and the differential diagnosis included an ovarian or a parovarian cyst. At laparotomy, a smooth thin-walled cyst was seen in the parovarium, attached to a short vascular pedicle. It was free of the ovary and tube and was easily shelled out by blunt dissection.

The cyst, measuring 10 cm. in diameter, contained clear serous fluid and was lined by a thin fibrous wall averaging 3 mm. in thickness. The inner lining was smooth over most of its surface with a few randomly scattered and focally clustered papillary ingrowths, which were firm, sessile, and dome shaped and varied from 2 to 5 mm. in width and height. The benign single-layered epithelium histologically resembled tubal epithelium (Fig. 1) and rested on dense, sparsely cellular fibrous tissue devoid of epithelial structures, smooth muscle, or ovarian stroma. The papillary ingrowths, lined by similar epithelium, consisted of cores of sparsely vascular, variably edematous fibrous tissue (Fig. 2). The epithelium of the cyst was identical tinctorially to that of the tube; no glycogen was detected, neutral and acid mucopolysaccharides were seen in individual cells at their luminal tips, and the basement membrane was rather indistinct.[1]

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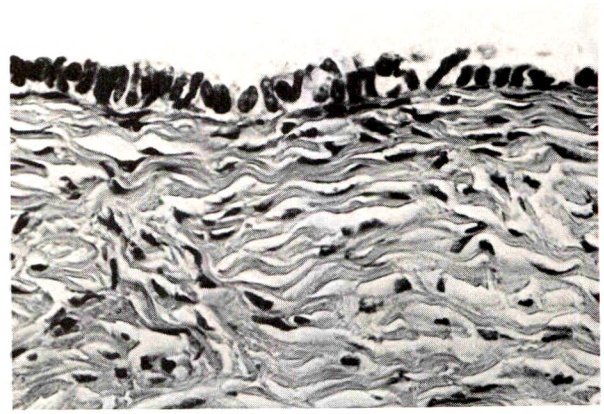


Fig. 1. Cyst wall. Benign single-layered ciliated epithelium resembling tubal epithelium. (Original magnification ×890.)



Fig. 2. Papillary ingrowths lined by single-layered epithelium and subtended by variably edematous fibrous core. (Original magnification ×55.)

This lesion clinically and pathologically fulfills the criteria of a papillary serous cystadenoma arising in a parovarian cyst.[1] Its paramesonephric origin is supported by the absence of smooth muscle in its wall, by its relatively indistinct basement membrane, and by the histologic and tinctorial similarity of its epithelium to

that of the oviduct.[1] Its exact site of origin is not apparent from the tissue examined but is most likely to be a focus of endosalpingiosis, i.e., heterotopic tubal epithelium in the parovarium.[1] The extreme rarity of secondary tumefaction in endosalpingiosis, as compared with that seen in endometriosis, is not surprising since endometrial epithelium has a far greater tendency to become hyperplastic, dysplastic, and carcinomatous. Malignancy confined to a parovarian paramesonephric cyst is exceptional,[3] though it is claimed, without formal proof, that, because of their proximity to the ovary and the absence of any tissue barrier to tumor spread in the parovarium, these cysts may be the original site of some of the widespread pelvic tumors usually interpreted as ovarian.

This growth is indistinguishable clinically from the usual parovarian cyst, and the diagnosis is only made pathologically.

Treatment by simple enucleation is curative, and no follow-up is indicated as the growth is nonrecurrent and has no significant association with any other gynecologic disorder.

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Salivary phosphate as an indicator of ovulation

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THE CONTINUING search for a simple but reliable method for detecting ovulation brought us to examine salivary changes during the menstrual cycle. Correlation between salivary composition and hormonal balance was reported in the literature.[1, 2] Salivary glucose and sialic acid concentration were considered as indicators of ovulation.[3, 4] In the present study, salivary phosphate concentration was measured. Correlation was found between the ovulatory status of women and the phosphate level.

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*Part of M.D. thesis.

Table I. Significance of the phosphate peak in ovulatory cycles of 14 women as determined by the t test

No.	*t*	*p*
1	7.802	<0.001
2	4.300	<0.01
3	3.196	<0.01
4	4.861	<0.001
5	8.365	<0.001
6	3.335	<0.01
7	3.598	<0.01
8	3.97	<0.002
9	7.69	<0.001
10	5.47	<0.001
11	3.87	<0.001
12	2.89	<0.02
13	3.38	<0.01
14	4.3	<0.002

Total mixed saliva was collected from 23 women of reproductive age (18 to 28 years old). Eighteen women had normal ovulatory menstrual cycles as determined by basal body temperature (BBT) monitoring. Five women were taking oral contraceptives. Four of the subjects were followed over two successive cycles.

The salivary samples were collected daily in the midcycle and every other day at the beginning and toward the end. The saliva was collected by a standard reproducible method. The collection always done during the morning, immediately after BBT measurement, to eliminate the effect of diurnal variation.[5]

The composition of saliva is different when it is produced spontaneously ("unstimulated") and by stimulation.[6] We preferred the spontaneous method. The subjects were instructed to let saliva accumulate in their mouth and then spit it out into a test tube. The saliva samples were placed in a refrigerator immediately after the collection, kept there during the cycle, and analyzed together at the same time. The samples were centrifuged and analyzed for phosphate by the sodium molybdate method.[7] The method was tested by repeating analysis of the same sample several times, and it was found to be accurate up to ±4 per cent.

The phosphate concentration of the saliva of 14 women with normal ovulatory cycles is presented in Figs. 1A and 1B. A peak at midcycle is evident in all cases. Statistical significance was estimated by the t test,[8] and the results are presented in Table I.

The salivary phosphate pattern was examined by collecting saliva over two successive cycles in the same

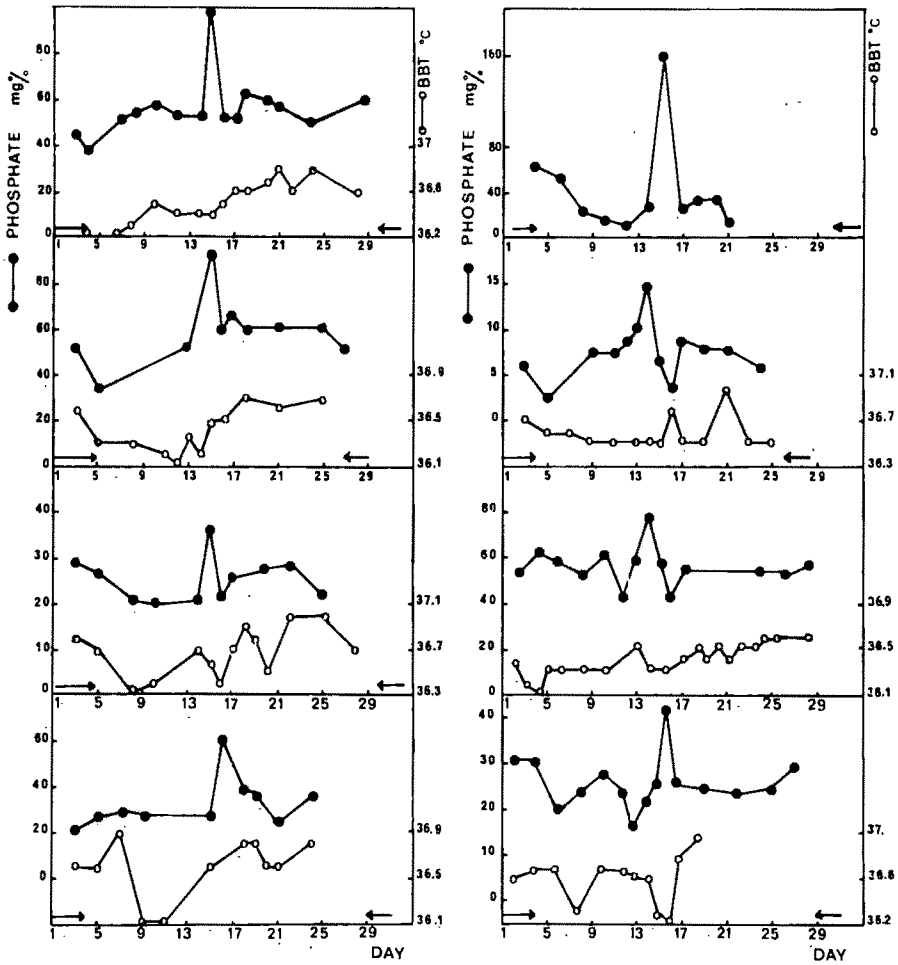


Fig. 1A. Salivary phosphate during menstrual cycles of eight women. The length of the cycle is indicated by the horizontal arrows.

women (four subjects). An illustration of two such cases is given in Figs. 2 and 3. In Fig. 2, the salivary phosphate concentration and BBT pattern are shown, and the similarity in the two-month period is striking. Fig. 3 shows a comparison of ovulatory and anovulatory cycles in the same woman. It indicates that a correlation between the BBT shift and the phosphate peak does exist.

As a negative control, saliva of five women using oral contraceptives was analyzed, and an illustration of phosphate concentration of one of these women is given in Fig. 4. The day-to-day fluctuation in phosphate is apparent, but no definite pattern can be seen. Another negative control is presented in Fig. 5. The phosphate concentration in a normal male subject shows a certain day-to-day variability.

The day-to-day fluctuations in the phosphate concentrations of anovulatory women and a man are small and express normal variability of salivary content (Figs. 4 and 5). However, this is insufficient to account for the significant peak in phosphate concentration repeatedly observed at midcycle (Figs. 1 to 3). The peak coincided with the BBT shift in 16 of 18 women analyzed. In two cases, the phosphate peak was doubtful.

No correlation between phosphate concentration in saliva and ovulation has been reported so far. Puskulian[1] analyzed phosphate of the parotid and submaxillary saliva and did not find a significant variation during the menstrual cycle. The reason might be that she worked on stimulated saliva, and it is known that stimulation affects salivary composition.[6]

The mechanism of phosphate secretion by the salivary glands is not yet clear,[9] but the consistent appearance of a phosphate peak at midcycle could not be incidental. The possibility that it implies hormonal regulation should be investigated. Further research correlating salivary phosphate with the menstrual cycle in a larger population and in comparison with a more accurate criterion of ovulation such as luteinizing hormone in the blood is planned.

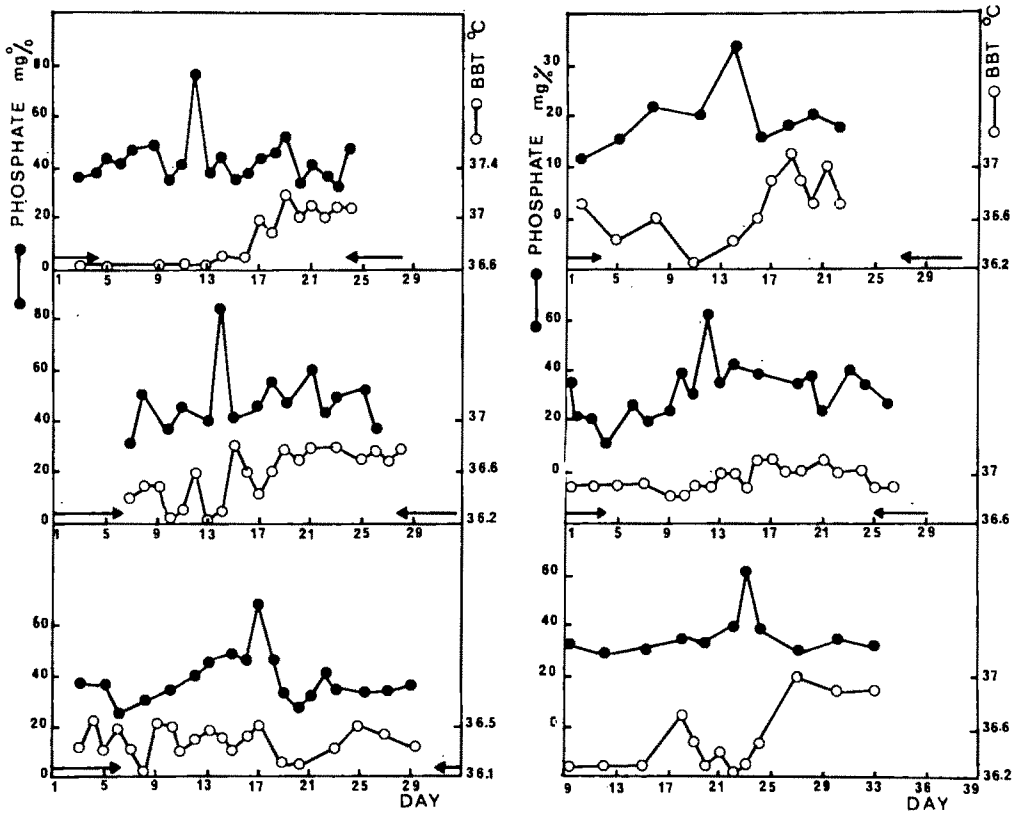


Fig. 1B. Salivary phosphate during menstrual cycles of six women. The length of the cycle is indicated by the horizontal arrows.

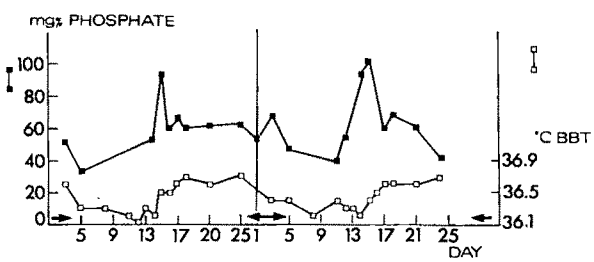


Fig. 2. Salivary phosphate and BBT in two successive menstrual cycles of one woman.

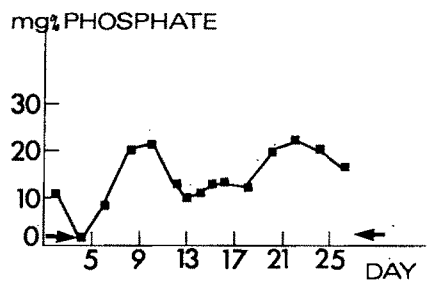


Fig. 4. Salivary phosphate concentration of a woman using oral contraceptives.

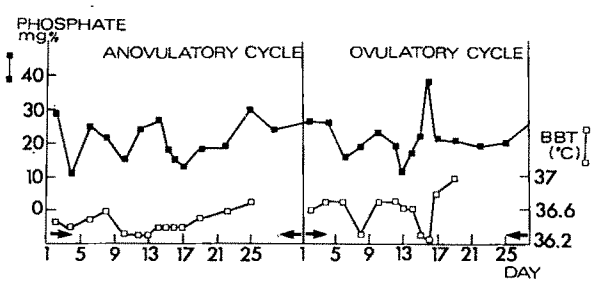


Fig. 3. Salivary phosphate and BBT in ovulatory and anovulatory cycle of one woman.

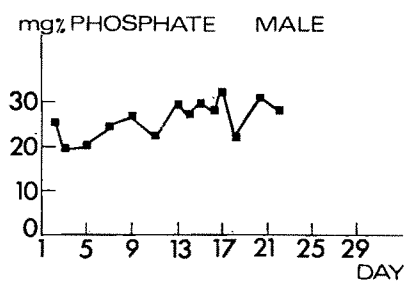


Fig. 5. Variation in salivary phosphate of a young male subject during one month.

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What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.



CORRESPONDENCE

Sterilization guidelines

To the Editors:

Dr. Raymond W. Rakow (AM. J. OBSTET. GYNECOL. 124: 215, 1976) is quite right! The need for sterilization guidelines to determine whether requests (for sterilization operations) will or will not be complied with *is* an attempt to impose male chauvinistic control over the life and reproduction of women and an infringement of their civil rights.

Documentation in the form of numerous court decisions attests to this fact (list available on request). Further, the right to control one's own body has been guaranteed by the United States Supreme Court in Roe vs. Wade and Doe vs. Bolton.

But over and above the court decisions guaranteeing individual freedom in matters of reproduction is an intrinsic human value used to measure a person's self-respect—the right to self-determination in choosing the way of life which offers the best opportunity for fulfillment of both personal and societal goals.

A doctor's role in a counseling situation is to explain all the facts, not to make moral judgments nor to intrude his personal prejudices. To pursue Dr. Rakow's reasoning one step further, one might logically conclude that women entering the menopause, having lost the functional option of potential generativity, are in danger of losing their self-esteem because they can no longer procreate.

To employ psychological standards which include self-hatred, self-contempt, rejection of gender, and self-mutilating motivation to characterize people seeking fertility termination is to arbitrarily impose one's own values on others and to display a prejudice toward childbearing and against women. It is unjustified in a pluralistic society such as ours.

The Association for Voluntary Sterilization has been able to be of service to many people seeking sterilization. They have been college professors, engineers, health professionals, white-collar workers, blue-collar workers, members of ethnic and religious minorities, the working poor, and the very poor. Sensible, sane, responsible people have been requesting and obtaining sterilization operations for a number of years and finding great relief and satisfaction knowing that they will not be faced with a financially and emotionally devastating unexpected pregnancy.

Doctors who are opposed to permanent methods of contraception should not be involved in the delivery of those services. Their personal rights include the exercise of conscience. However, their obligations as participants in public health programs do include responsibility for making certain those services are available to their patients.

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First excision of the uterine cervix

To the Editors:

It is always a near fatal challenge to claim a "First." Therefore, I am forwarding this information not necessarily as a "First" but simply as a historical fact.

Dr. Horatio Gates Jameson, who received his M.D. from the University of Maryland in 1813, is credited by local historians with excision of the uterine cervix in 1824, about five years prior to Strachan's case (AM. J. OBSTET. GYNECOL. 124: 97, 1976). Jameson, apparently an intrepid surgeon, also extirpated an entire upper jaw in 1820 and performed a tracheotomy for the first time in Baltimore in 1818.

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Transplacental mumps infection

To the Editors:

A previous study from this laboratory (AM. J. OBSTET. GYNECOL. 119: 549, 1974) did not support the contentions of the relative frequency of congenital involvement by mumps virus and the concept of split immunity as proposed by Aase and associates[1, 2] and St. Geme and colleagues.[3] The recent report by Drs. Chiba, Ogra, and Nakao (AM. J. OBSTET. GYNECOL. 122: 904, 1975) on the failure to: (1) recover mumps virus from multiple fetal organs, and (2) demonstrate the presence of immunoglobulin M (IgM)–specific antibodies in a conceptus whose mother's gestation had been complicated by mumps infection, contributes a vital missing observation, namely, a virologic as op-

posed to a predominantly immunologic documentation of noninvolvement.

I would like to throw one more pebble into this sea of controversy, namely, the occurrence of clinical mumps in an infant born to one of the mothers whose gestation had been complicated by maternal infection and who was part of the original study.

L. G., a 21-year-old, black primigravida, presented at 94 days' gestation with fever and bilateral parotid gland enlargement. The patient denied prior mumps infection or vaccination. The availability of serum obtained at her initial prenatal visit and two weeks after convalescence revealed a greater than sixteenfold increase in the hemagglutination-inhibition (HAI) titer as determined by the microtechnique (with the use of 8 u. of antigen). Following recovery from this illness, the patient had an uneventful gestation and delivered five days beyond the expected date of confinement.

The progeny, F. B., was a well-developed, well-nourished male infant whose birth weight was 2,700 grams. The cord IgM level, determined by means of a single radial immunodiffusion technique with IgM immunoplates and standards,* was 17 mg. per 100 ml. The infant was seen at six-month intervals and remained in about the seventy-fifth percentile in terms of growth and development. There has been no evidence of cardiovascular involvement at any time. At 270 days of age, follow-up titers failed to reveal evidence of antibody synthesis while a persistent HAI titer of 1:64 was still demonstrable in the maternal serum. Approximately one week after these determinations, the infant was given 1 c.c. of formalin-killed vaccine by intramuscular injection. Three weeks later, a HAI titer of 1:64 was demonstrable in the serum.

At 37 months of age, the infant presented as a well-developed, well-nourished, black male infant in no acute distress but with right parotid gland swelling. The temperature was 100.6° F. Pair sera were obtained at the time of initial examination and two weeks later. The initial titer was 1:2 and subsequently rose to 1:64.

This case is of interest because the child acted at his own biological indicator system, thus negating a possibility of split-immunity functioning. Because this is an isolated observation, the implied thesis of nontransmission should be either substantiated or placed in statistical perspective by additional observations.

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Ectopic pregnancy after postcoital diethylstilbestrol

To the Editors:

The report of Drs. A. R. Smythe II and P. B. Underwood, Jr. (121:284, 1975), attributes the ocurrence of a tubal pregnancy to failure of high doses of postcoital stilbestrol to prevent pregnancy. This assumption is almost certainly erroneous. In a series of papers, my associates and I[2–4] presented irrefutable evidence, including basal body temperature charts taken during cycles of fertilization, which indicated that ectopic conception with few exceptions precedes, not follows, the patient's last recorded menstrual period. In other words, at the time of the "condom accident," in the authors' reported case, on Day 14 of the cycle the patient must have been pregnant for about three weeks.[4]

Significantly, all previously reported "method failures" with diethylstilbestrol that had been reviewed by the authors had apparently resulted in ectopic gestation. In view of current knowledge concerning the pathologic mechanism of extrauterine pregnancies, this observation indicates that the drug, if given in adequate doses and at the appropriate time, invariably prevents pregnancy.

The association of ovulation defects and their accompanying phenomena with various pathologic conditions of gestation is a very interesting problem that has been in the center of interest of prominent reproductive biologists in recent years.[1, 5, 6] Therefore, it is unfortunate that obstetricians continue to ignore the relevant data[7] despite their considerable academic and clinical significance.

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Reply to Dr. Iffy

To the Editors:

In reply to Dr. Iffy's letter regarding ectopic pregnancies after postcoital diethylstilbestrol, I disagree with both of his points. The duration of time from this patient's last menstrual period until a positive pregnancy test was seven weeks and five days and exactly nine weeks until the time of tubal rupture. From Dr. Iffy's theory, she would have been 13 weeks pregnant. The abortion was a tubal abortion with an intact tubal serosa and no grossly recognizable fetus.

I do agree that a woman may have normal menses with a developing tubal pregnancy but certainly not always. In this patient, the condom accident was followed in the proper time sequence by missed menses, symptoms of pregnancy, a positive pregnancy test, and then the tubal abortion. For these reasons, I believe that the date of nine weeks from the last menstrual period is the more accurate gestational age.

As for Dr. Iffy's second point that stilbestrol invariably prevents pregnancy, evidence strongly opposes this, as illustrated in this case and the review of the 9,000 exposures reported by Dr. John Morris as referred to in the original manuscript. I do agree that a Pearl index of 0.4 indicates a highly successful means of preventing pregnancy.

I appreciate the opportunity to answer Dr. Iffy's letter and regret that I disagree with him; however, disagreements usually enlighten all parties involved and make medicine a challenging frontier.

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Potential dangerous complication of the ballooned uterine elevator cannula

To the Editors:

I would like to comment on a potential dangerous complication in using the ballooned uterine elevator cannula introduced by Dr. Hasson in the November 15, 1975, issue of the JOURNAL, on page 658.

We have observed two uterine fundal perforations with this instrument in the course of uterine manipulation during laparoscopy. We reasoned that the perforation occurred in the following manner: A Foley catheter of slightly excessive length was threaded tightly onto the metal cannula. In the process of manipulation, the catheter folded over the tip of the metal canula at a point *behind* the balloon. The relatively "sharp" metal tip covered with the catheter then perforated the fundus—carrying the balloon with it. Neither of these patients had recently been pregnant, and the perforation occurred with surprising ease.

Readers who plan to use this instrument should exercise care in using a Foley catheter of appropriate length to ensure that the balloon is over the metal tip. An overenthusiastic technician might easily thread the catheter so tightly that it "bunches" on the metal cannula. These "bunches" later loosen, placing the balloon in front of the metal tip.

This possibility was not adequately explored in the original article.

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The hypothalamus and reproduction

To the Editors:

In a recent review, Dr. Schally and co-workers (AM. J. OBSTET. GYNECOL. 122: 857, 1975) commented that patients with the Stein-Leventhal syndrome (SLS) exhibit a normal response to luteinizing hormone–releasing hormone (LH-RH) as was found by Zarate and associates.[1] These authors found no significant difference in pituitary response to intravenous administration of 50 μg of synthetic gonadotropin-releasing hormone (Gn-RH) between six patients with SLS and 10 normal menstruating women.

However, other investigators, including ourselves, have recorded LH responses to LH-RH in patients with polycystic ovaries (PCO) which are at variance with the results of these investigators. Aono and associates[2] found an exaggerated LH response in five of six patients with PCO. Patton and co-workers[3] recorded elevated responses in 14 of 17 patients with this condition. All eight patients who had enlarged ovaries and six of nine patients with normal-size polycystic ovaries had elevated LH values 30 minutes after LH-RH injection, which exceeded the arbitrary normal response. Duignan and associates[4] found the mean LH response to be similar to that found in the luteal phase of ten normal control subjects but significantly greater ($P < 0.02$) than that found in the early follicular phase of the cycle.

We have found that within the PCO "hodgepodge,"

two distinct groups can be defined according to basal LH levels and LH response following LH-RH. Group 1 patients have elevated basal LH levels and an exaggerated delayed response to LH-RH, while Group 2 patients have normal basal LH levels and a quantitatively normal LH response.[6]

All of the above investigators, with the exception of Zarate and associates,[1] administered 100 μg of LH-RH which might explain the discrepancy in results. On the other hand, it may be that all six of the patients of Zarate and associates belong to our PCO Group 2.

The detection of two groups of patients with polycystic ovaries is important. It may be that they represent different pathophysiologic conditions or, alternatively, that Group 1 is merely a more advanced stage of the same condition existing in Group 2. Either way, the detection of two groups is exciting, as 40 years since the original description of the Stein-Leventhal syndrome[6] controversy still exists regarding its etiology.

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Abnormal glucose tolerance tests and infant outcome

To the Editors:

In the article by Drs. Haworth and Dilling on abnormal glucose tolerance in pregnancy and infant mortality and morbidity rates (Am. J. Obstet. Gynecol. 122: 555, 1976), they conclude that ". . .documentation of the degree of glucose intolerance. . .is of little value in assessing fetal outcome." They also note that neither the oral nor intravenous glucose tolerance test is of value in assessing fetal outcome. The two mothers having stillbirths in their study also had abnormal intravenous glucose tolerance tests. Since the frequency of abnormal intravenous tests is not given, the questions raised are:

1. How many abnormal intravenous tests occurred?
2. How were the abnormal intravenous tests related to the abnormal oral tests?
3. Was the fetal death rate higher in women with abnormal intravenous tests than in either the control population or those with normal intravenous tests?
4. Are the authors recommending on page 560 and in the abstract that glucose tolerance tests on pregnant women be abandoned if the fasting blood glucose value is normal?

Finally, one woman was treated with tolbutamide and, since it affects fetal insulin secretion and survival, was that case excluded from the cord insulin calculations and what was the outcome of that gestation?

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Reply to Dr. Spellacy

To the Editors:

The answers to Dr. Spellacy's questions about our article are as follows:

1. Of the 84 intravenous glucose tolerance tests, 47 were normal, and 37 were abnormal.
2. Eight of the 16 women with diabetic oral glucose tolerance tests also had intravenous tests; seven of these intravenous tests were abnormal, and one was normal. Both oral and intravenous tests were normal in 46 women. Thirty women had abnormal intravenous tests but normal oral tests. Dyck and Moorhouse,[1] whose method for the intravenous test was used, have discussed the usefulness and sensitivity of the intravenous test as an indicator of abnormal carbohydrate metabolism as compared to the oral test.
3. We do not have information about the total fetal wastage among the women in our small series. There were two stillbirths, both in women with abnormal intravenous tests but with normal oral tests. The stillbirth rate among women with abnormal intravenous tests was not significantly different from that in women with normal intravenous tests or from that in our over-all hospital group. However, numbers of observations were small.
4. We did not recommend that glucose tolerance tests should be abandoned in pregnant women if the fasting blood glucose value is normal. What we said was that our study suggested that the results of glucose tolerance tests were of little value in predicting fetal outcome, although they may indicate infants at risk of hypoglycemia and hypocalcemia. Recently we[2] have shown that the probability of neonatal hypoglycemia can be predicted from the mother's glucose level two hours following the oral glucose tolerance test. We recognize that there may be several reasons for an obstetrician to perform a glucose tolerance test on a pregnant woman who is at risk for diabetes.

The infant of the mother who was treated with tolbutamide was normal at birth and did not have

hypoglycemia. The umbilical cord blood insulin level of this infant was 20 μU per milliliter, which was close to the mean insulin level of the infants of nondiabetic mothers (see Table II of the original article).

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Recording of birth injuries and malformations of the infant

To the Editors:

I have read the report in the October 1, 1975, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in which it is pointed out that on the birth certificate obstetricians report "complications of pregnancy and delivery" as often as do general practitioners, but general practitioners report "birth injuries and malformations" three times as often as do obstetricians. The article concluded that this was probably due to diagnostic error, differences in types of patients seen, and differences in delivery techniques that had a real impact on subsequent morbidity. I would like to offer an alternative explanation.

Obstetricians view the mother as their primary patient and infrequently see the infant after it leaves the delivery room. Very frequently, a pediatrician or some other physician examines the newborn infant. The general practitioner views both the mother and the infant as his patients and examines both of them after they leave the delivery room. Thus, the obstetrician and general practitioner have similar opportunity to notice and record complications of pregnancy and labor, but the general practitioner is more likely to observe and record birth injuries and malformations of the infant. Thus, I would suggest that the differences studied are not differences in incidence rates but in rates of observation and reporting.

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Safety of lincomycin in pregnancy

To the Editors:

In completing their study on the safety of lincomycin in pregnancy, Drs. Mickal and Panzer have made a rare contribution to medicine. Prospectively studying some 300 pregnant women, they have shown that a seven-day course of lincomycin, 2 Gm. per day orally, poses no detectable risk of fetal malformation or delayed developmental defect in childhood. Extending their results to clindamycin seems a little risky without an independent study, but at least physicians wishing to use lincomycin in pregnancy now have a study to point out in case questions of safety arise.

As the authors stated, all newly developed drugs are now being marketed with the admonition that safety in pregnancy has not been established. The dilemma is obvious. Pregnant women do become ill and sometimes require medication. The newer drugs are not certified as safe, yet there is no clear-cut way to establish safety in human subjects unless a life-threatening maternal infection is involved for which no alternative therapy is available. The accumulated case histories of hundreds of such women could eventually be collated in a retrospective study, but such a study would certainly not fulfill the criteria for unbiased safety testing. On the other hand, what woman, having been fully informed of the potential risks, would volunteer her unborn child to prove that a benign disease safely can be treated in pregnancy with a drug for which alternatives with established safety records are available?

The patients of Drs. Mickal and Panzer appear to have done just that. A review of their two publications on this study (South. Med. J. 59: 567, 1966; AM. J. OBSTET. GYNECOL. 121: 1071, 1975) does not reveal how these women were motivated to participate.

To help fulfill the hope ". . . that the publication of these results will encourage other medications to be so studied," the authors should suggest guidelines for ethical recruitment of patients. These guidelines will need to anticipate, among other things, the lawsuit brought by a deformed child against his/her mother (and the physician investigator).

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BOOKS

Books received

Clinical Cancer Chemotherapy. Edited by Ezra M. Greenspan. 431 pages, illustrated. New York, 1975, Raven Press, Publishers. $16.50.

New Health Practitioners. John E. Fogarty International Center Series on the Teaching of Preventive Medicine. Vol. 1. Edited by Robert L. Kane. 156 pages, illustrated. Washington, D. C., 1975, United States Government Printing Office. (Department of Health, Education, and Welfare Publication No. NIH 75-885.) Price not available.

Obesity in Perspective. John E. Fogarty International Center Series on Preventive Medicine. Vol. 2, Part 2. Edited by George A. Bray. 527 pages, illustrated. Washington, D. C., 1975, United States Government Printing Office (Department of Health, Education, and Welfare Publication NIH 75-708.) $9.90.

Only Human: Teenage Pregnancy and Parenthood. Marion Howard. 261 pages. New York, 1975, The Seabury Press, Inc. $8.95.

Pathology of the Fetus and the Infant. Ed. 3. E. L. Potter and J. M. Craig. 697 pages, illustrated. Chicago, 1975, Year Book Medical Publishers, Inc. Price not available.

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Prostaglandins and Reproduction. Edited by S. M. M. Karim. 332 pages. Baltimore, 1975, University Park Press. $29.50.

Pulmonary Physiology of the Fetus, Newborn and Child. Edited by Emile M. Scarpelli. 369 pages, illustrated. Philadelphia, 1975, Lea & Febiger, Publishers. Price not available.

Risks in the Practice of Modern Obstetrics. Ed. 2. Silvio Aladjem. 425 pages, illustrated. St. Louis, 1975, The C. V. Mosby Company. $32.50.

Vascular Surgery. Vol. II. Peripheral Venous Diseases. John J. Cranley. 368 pages, illustrated. Hagerstown, Maryland, 1975, Harper & Row, Publishers. $37.50.

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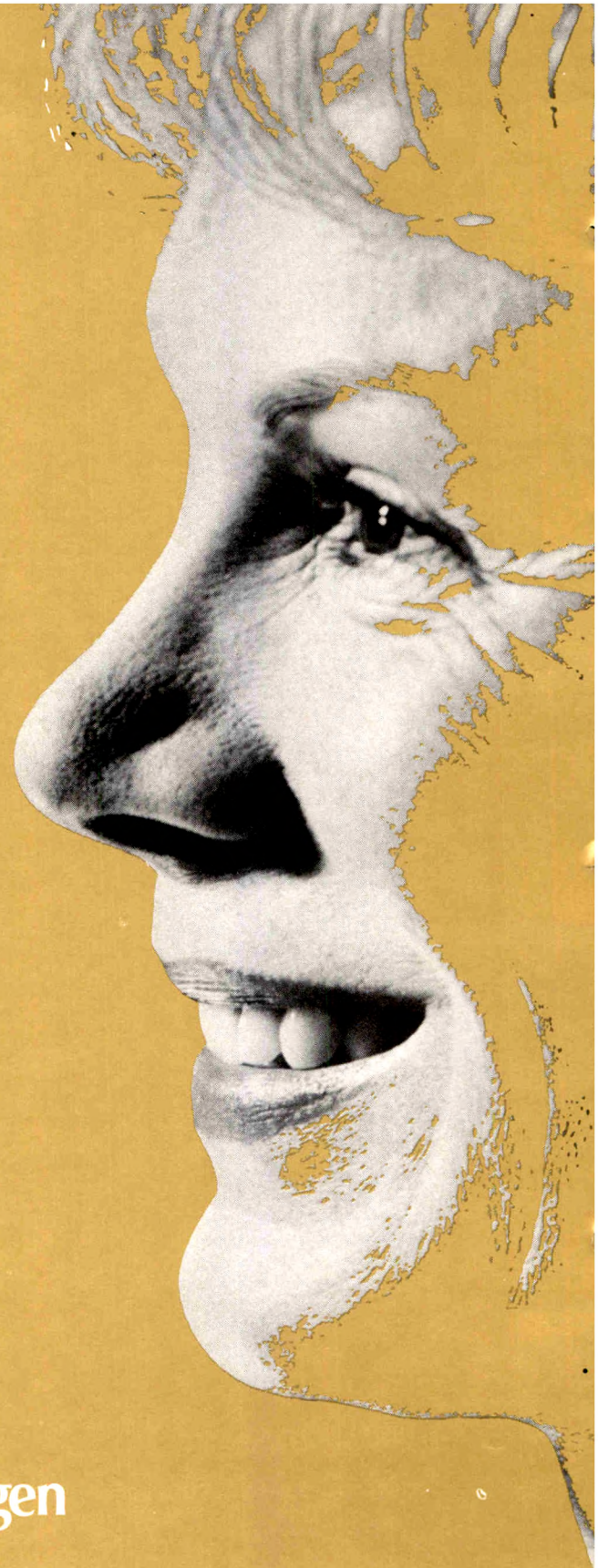
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Estrogen replacement therapy moves forward



the major human estrogen micronized for oral effectiveness

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(estradiol)

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- estradiol...the active estrogen at the cellular level

from Mead Johnson

overall, 95% of patients studied gained adequate or complete relief of their symptoms[1]

Estrace (estradiol) was given to 369 estrogen-deficient women for periods ranging up to a year or more (average of six months); 319 of these women received an initial dosage of 1 or 2 mg. per day and were evaluated for efficacy. *Complete disappearance* of hot flushes was experienced by 227 (76%) of 298 women, of sweating by 131 (80%) of 164 women, of tingling by 62 (94%) of 66 women, and of genital atrophy by 44 (88%) of 50 women. In general, 95% of the patients evaluated experienced either adequate or complete relief of their symptoms. Remarkably, in 77% of the patients, symptoms were controlled without need to adjust the initial dosage—usually 2 mg. daily. (Dosage after adjustment ranged from 1 mg. to 3 or 4 mg. a day.)[1]

cyclic therapy recommended

Recently, published reports of retrospective human data have emphasized that patients using estrogens may have an associated increased risk of endometrial cancer. This information makes cyclic rather than continuous estrogen replacement therapy even more prudent. (See brief summary.)

With Estrace, treatment should be initiated with a dose of 1 or 2 mg. daily and then adjusted to the lowest dose possible still maintaining the relief of symptoms. The usual regimen for cyclic administration of Estrace is three weeks on drug, followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4–6 days) to prevent recurrence of menopausal symptoms.

estradiol... orally effective

The technique of micronization has opened up the oral route to natural human estrogen replacement with Estrace. Reduced particle size of the estradiol in Estrace makes effective gastrointestinal absorption possible. Onset of action is rapid, with marked increases in levels of circulating estradiol and estrone; concomitant decreases in serum concentrations of FSH and LH are sustained over a 24-hour period.[2]

Because estradiol can be assayed in plasma, Estrace can provide objective[2] as well as clinical evidence[1] of ready availability and biologic activity.

well accepted by patients[1]

In the 369 patients previously described, the incidence of estrogen-induced side effects with Estrace was relatively low. Incidence of nausea was remarkably low—only 2% of patients before dosage adjustment. Some patients who had complained of this problem while on conjugated equine estrogens reported its complete disappearance on changing to Estrace. Whereas before dosage adjustment 24% experienced breast tenderness, 31% edema, 18% (of 151 with intact uteri) bleeding, and 4% weight gain, only about 2% of the 369 patients dropped out because of side effects.[1]

long-term therapy should be monitored

A few instances of significant gynecologic disease became apparent during clinical investigations.[1] Endometrial hyperplasia was discovered in seven patients, all of whom had previously received estrogen therapy for one to three years prior to entering the study. One patient was reported to have carcinoma *in situ* and another showed adenocarcinoma of the endometrium. In clinical practice, the physician should be alerted to the potential of thrombotic disorders and be prepared to discontinue medication immediately if they occur. Because of variations in normal endogenous hormone production, certain patients may exhibit signs of excessive estrogenic stimulation. Adverse reactions generally associated with estrogen administration may occur and these are listed in the brief summary. Prior to initiation of treatment with Estrace or any other estrogenic preparation, an adequate physical examination should be given.

References

1. Callantine, M.R., *et al.*: Micronized 17β-estradiol for oral estrogen therapy in menopausal women, Obstet. Gynecol. *46*:37–41 (July) 1975.
2. Yen, S.S.C., *et al.*: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β-estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. *40*:518–521 (March) 1975.

For Brief Summary, please see following page.

Estrogen replacement therapy moves forward...

Estrace® (estradiol)

the major human estrogen micronized for oral effectiveness



Indications: Estrace® (17β-Estradiol) is indicated for relief of endogenous estrogen deficiency and associated menopausal symptoms.

Contraindications: Estrace® is contraindicated in patients with 1) markedly impaired liver function; 2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible; 3) known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium; 4) undiagnosed abnormal genital bleeding; 5) thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions; and 6) pregnancy.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen medication should be stopped. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

Adverse Reactions: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis). The following adverse reactions are known to occur in patients receiving estrogens: nausea, vomiting, anorexia, gastrointestinal symptoms (such as abdominal cramps or bloating), edema, breakthrough bleeding, spotting or withdrawal bleeding, breast tenderness and enlargement, change in body weight (increase or decrease), headache, increased cervical mucus, allergic rash, loss of libido and gynecomastia in the male, reactivation of endometriosis, aggravation of migraine headaches, hepatic cutaneous porphyria becoming manifest, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, cystitis-like syndrome, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, possible diminution in lactation when given immediately post-partum, irritability, and malaise.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than nonusers to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study. In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients. Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued. It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

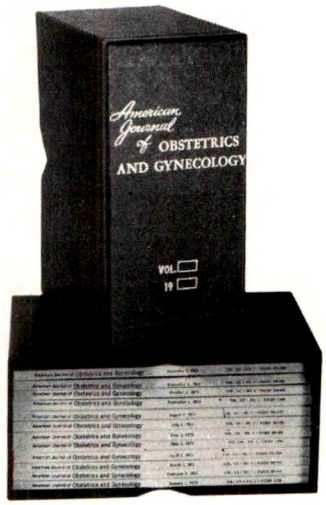
(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Childbearing Age. Brit. Med. J., 2:193-199, 1968. (3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969. (5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970. (6) Herbst, et al. — Adenocarcinoma of the Vagina — New England Journal of Medicine, Vol. 284, Number 16 (April 22, 1971).

Dosage and Administration: Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol. Dosage may be adjusted to control the presenting symptoms depending on the response of the individual patient; the minimal effective dose for maintenance therapy should be determined by titration. To avoid continuous stimulation of the reproductive tract and breasts, cyclic therapy is recommended. The usual regimen consists of three weeks on drug followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4-6 days) to prevent recurrence of menopausal symptoms. Withdrawal bleeding of unusual amount or duration should be investigated.

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The woman profiled here is an actual ZORANE 1/50 user. However, not all women can be expected to have the same tolerance for side effects, should any occur. (Data on file, Lederle Laboratories)

*Dropout rates are based on total patient population (1,156); incidence reflects only those patients who completed one or more cycles (956).

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Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of sequential products appears to be somewhat lower than that of combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons, as observed in clinical trials, with ZORANE 1.5/30 appears to be the same as that of higher dose combination products. The dropout rate due to irregular bleeding was somewhat higher, but dropouts were equally split between irregular bleeding and other medical reasons attributable to the drug. (ZORANE 1/20 only: The effectiveness is somewhat lower than that of the higher dose combination products. Both provide almost completely effective contraception. Dropout rate for medical reasons appears to be somewhat higher than with higher dose combination products, due particularly to irregular bleeding.) An increased risk of thromboembolic disease associated with use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, reduced tolerance to carbohydrates, have not been quantitated with precision. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. Possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indications: For control of conception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen-dependent neoplasia; undiagnosed abnormal genital bleeding; pregnancy.

Warnings: If early signs of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis) occur or are suspected, discontinue use of drug immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug stoppage and not enhanced by long-term use.[1-4]) If sudden partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Safety of use in pregnancy has not been established, therefore rule out pregnancy in any patient who has missed two consecutive periods before continuing contraceptive regimen; if prescribed schedule has not been adhered to, consider possibility of pregnancy with first missed period. A small fraction of hormonal agents has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant has not yet been determined.

Precautions: Pretreatment and periodic physical examinations of breasts and pelvic organs should include Papanicolaou smear. (Estrogens have produced tumors, some malignant, in 5 species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after drug withdrawal for 2 months. With use of these drugs, pre-existing uterine fibromyomata may increase in size; and some conditions (*i.e.*, epilepsy, migraine, asthma, cardiac or renal dysfunction) may be influenced by fluid retention; observe carefully for such. With use of ZORANE 1.5/30 or ZORANE 1/20, alteration in menstrual patterns may be induced. Since the amount and duration of flow and cycle length may vary, this must be considered in attempting to determine if cause of bleeding is organic. (ZORANE 1/50 only: In breakthrough bleeding or all cases of irregular bleeding per vaginam, keep in mind nonfunctional causes and take adequate diagnostic measures.) With history of psychic depression, discontinue drug if depression recurs to a serious degree. Possible influence of prolonged ZORANE therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been seen in some patients on oral contraceptives; carefully observe diabetics on such therapy. Patient age is no absolute limiting factor, although these drugs may mask onset of climacteric. The pathologist should be advised of ZORANE therapy when relevant specimens are submitted. Susceptible women may have an increase in blood pressure following use of contraceptive steroids.

Adverse Reactions Observed in Patients Receiving Contraceptives: Statistically significant association demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis. Suggestive evidence, neither confirmed nor refuted, between use and neuro-ocular lesions (*e.g.*, retinal thrombosis, optic neuritis). Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps, bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), weight change (increase or decrease), changes in cervical erosion and secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible women, mental depression. Reported association with use, neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching. *May Alter Laboratory Results in:* hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX, X), thyroid function (increase in PBI_1, and butanol extractable protein bound iodine, and decrease in T^3 uptake values), metyrapone test, pregnanediol determination.

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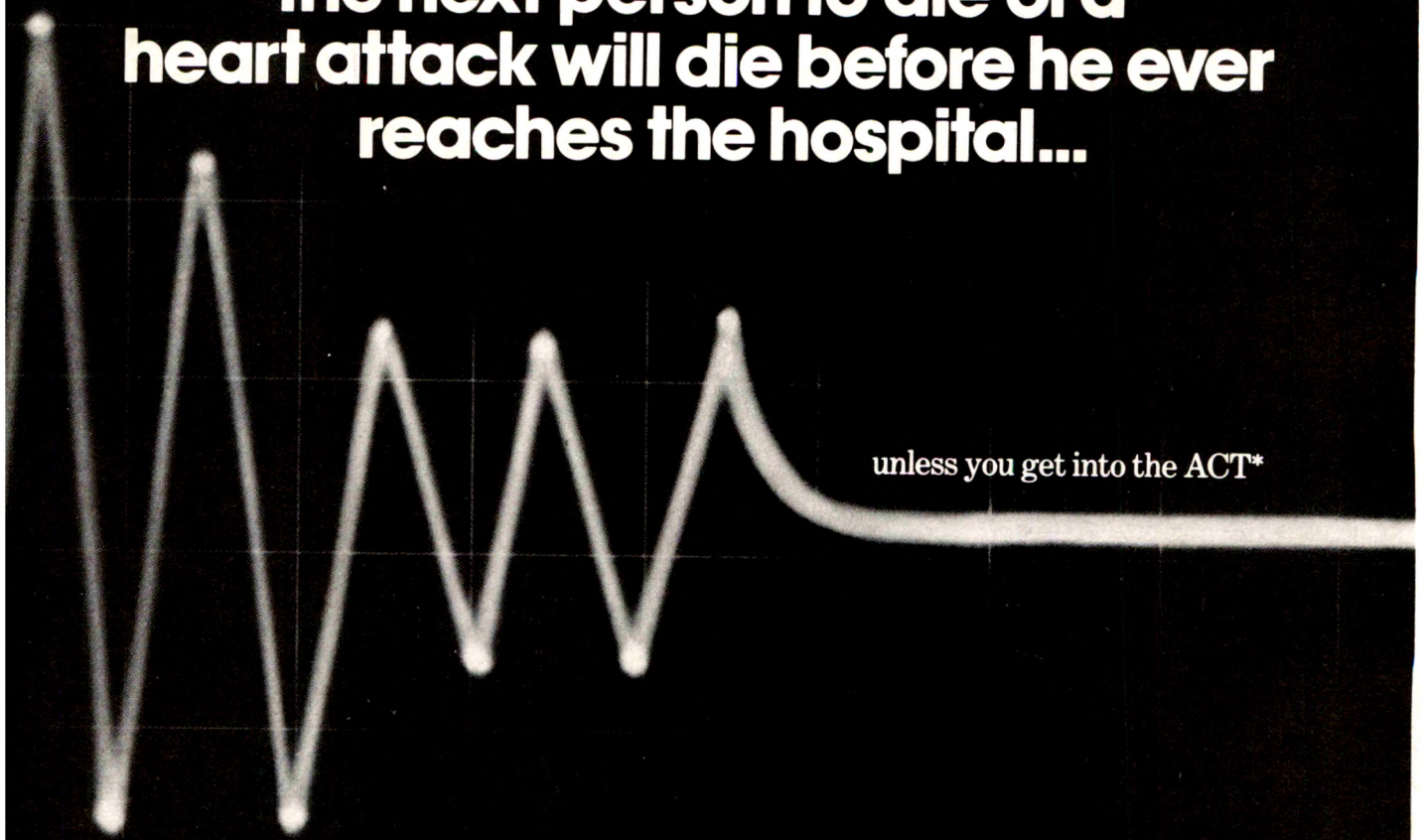
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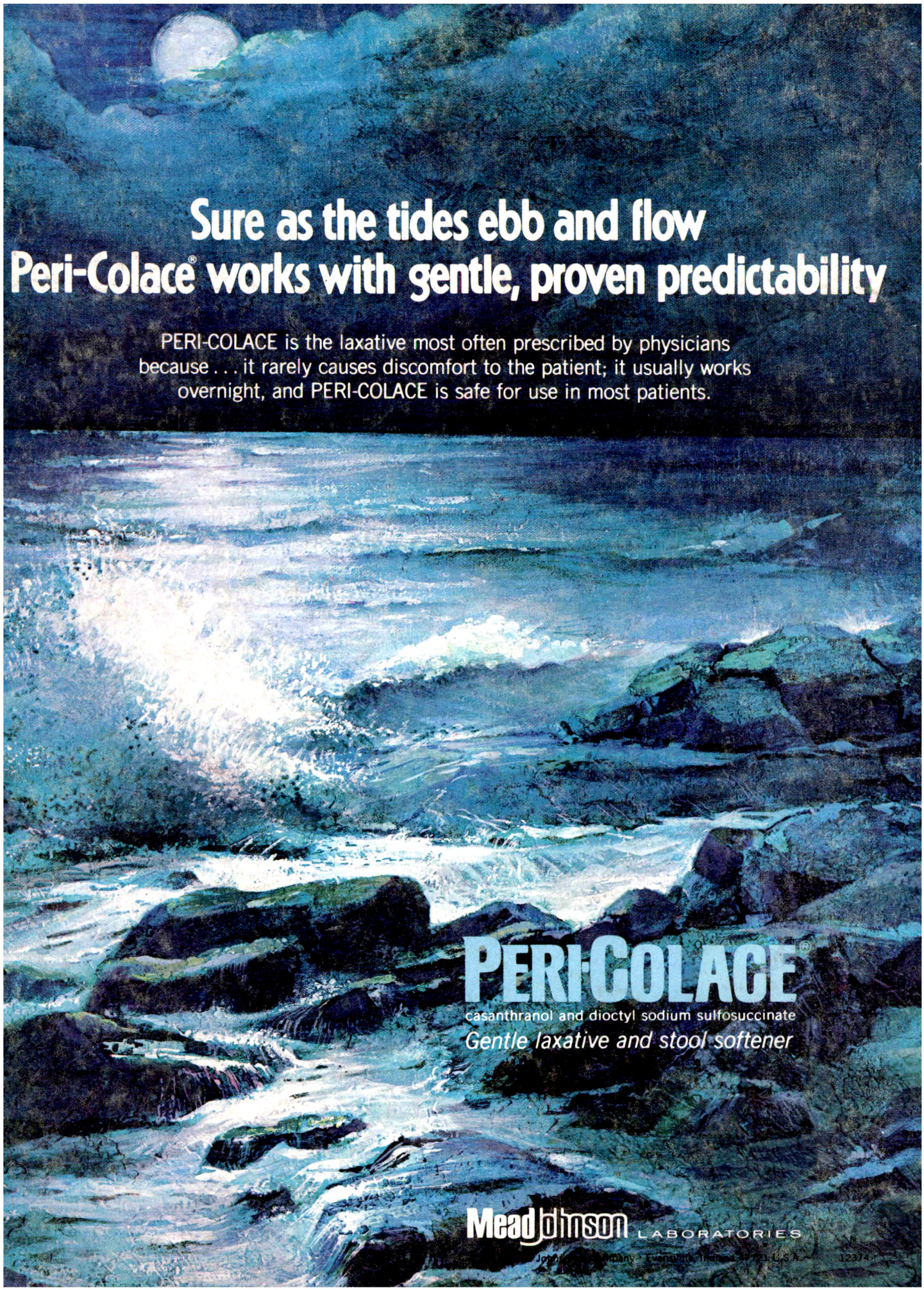
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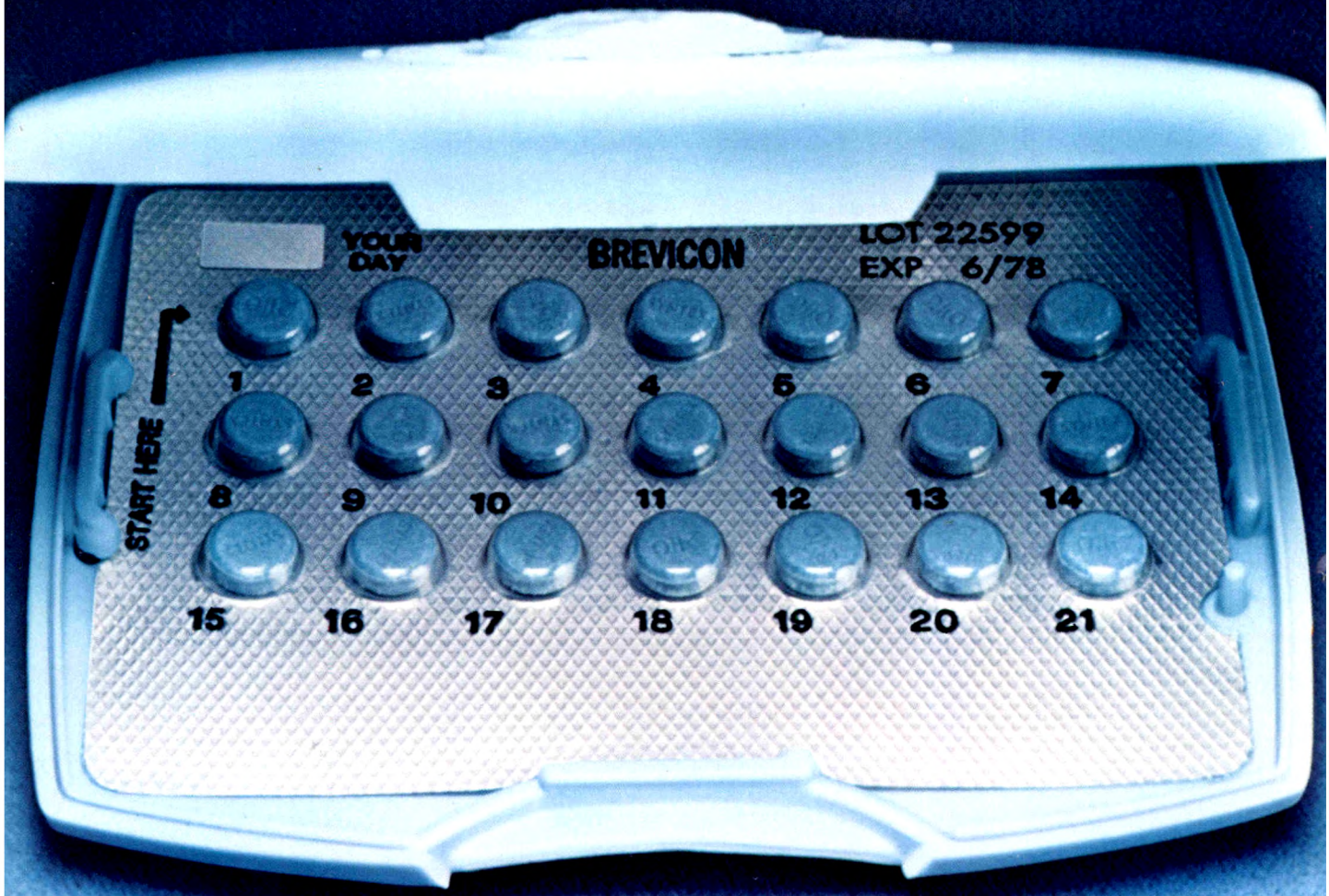
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Effectiveness and low hormonal intake



Effectiveness

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SYNTEX

Effectiveness and low hormonal intake

Summary of prescribing information

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with BREVICON®, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

BREVICON tablets are indicated for oral contraception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestation of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

   Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1, 2, 3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.
2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
3. Since the safety of BREVICON tablets in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.
4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.
5. Hepatic cell adenomas have been reported in women on oral contraceptives. The adenoma may present as an abdominal mass or with the signs and symptoms of an acute abdomen. A bleeding hepatic cell adenoma should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to liver, breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.
2. Endocrine and possibly liver function tests may be affected by treatment with BREVICON tablets. Therefore, if such tests are abnormal in the patient taking BREVICON tablets, it is recommended that they be repeated after the drug has been withdrawn for two months.
3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.
4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.
6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
7. Any possible influence of prolonged BREVICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.
8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving BREVICON therapy.
9. The age of the patient constitutes no absolute limiting factor, although treatment with BREVICON tablets may mask the onset of the climacteric.
10. The pathologist should be advised of BREVICON therapy when relevant specimens are submitted.
11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

thrombophlebitis, pulmonary embolism, cerebral thrombosis.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives:

nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes: tenderness, enlargement and secretion, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by the use of oral contraceptives:

hepatic function: increased sulfobromophthalein retention and other tests, coagulation tests: increase in prothrombin factors VII, VIII, IX and X, thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values, metyrapone test, pregnanediol determination.

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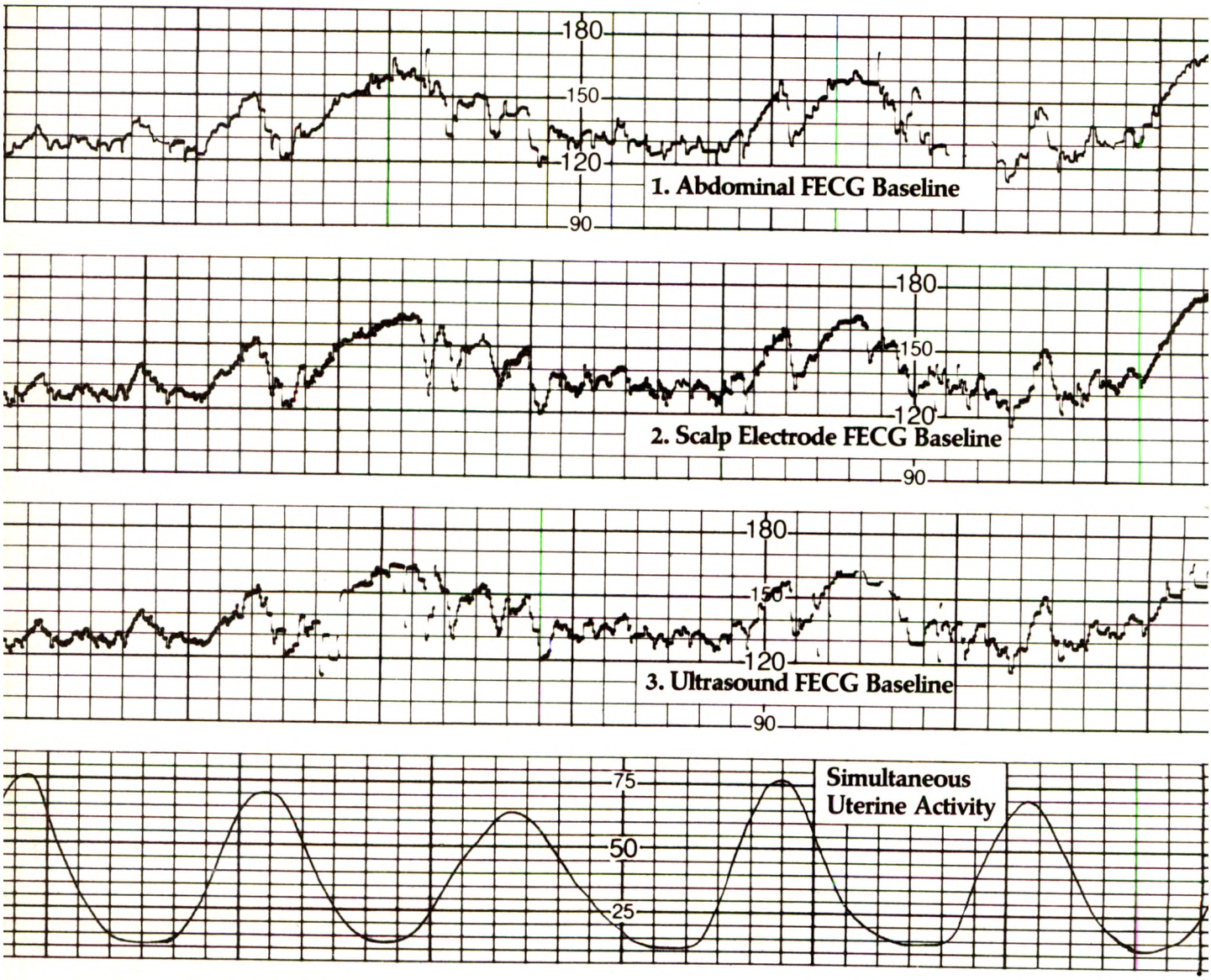
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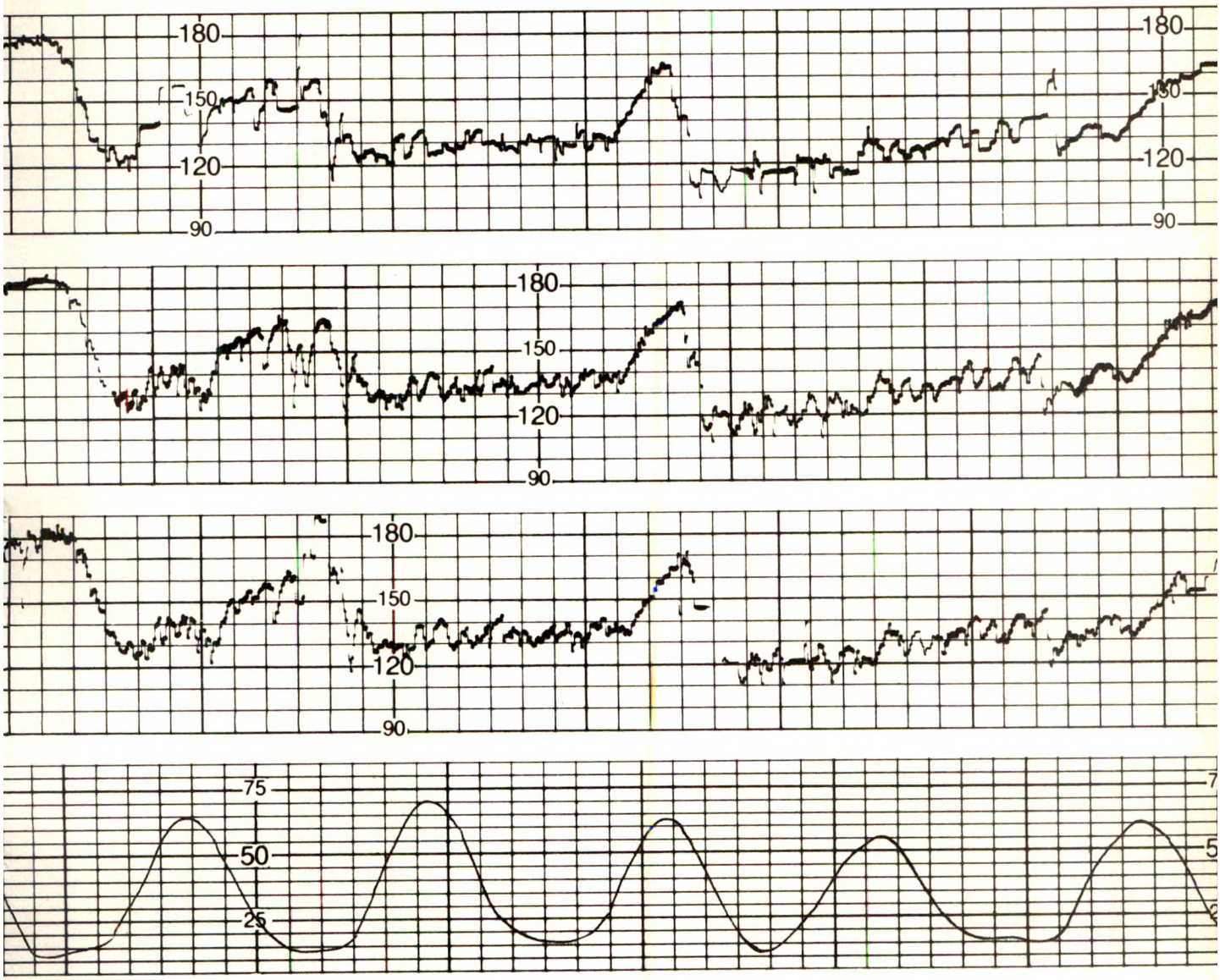
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"Possibly" effective: For the treatment of trichomoniasis, vulvovaginal candidiasis, and vaginitis due to *Hemophilus vaginalis* or other susceptible bacteria.

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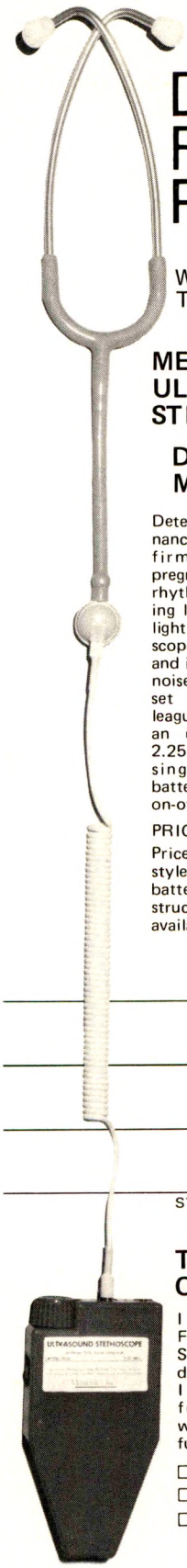
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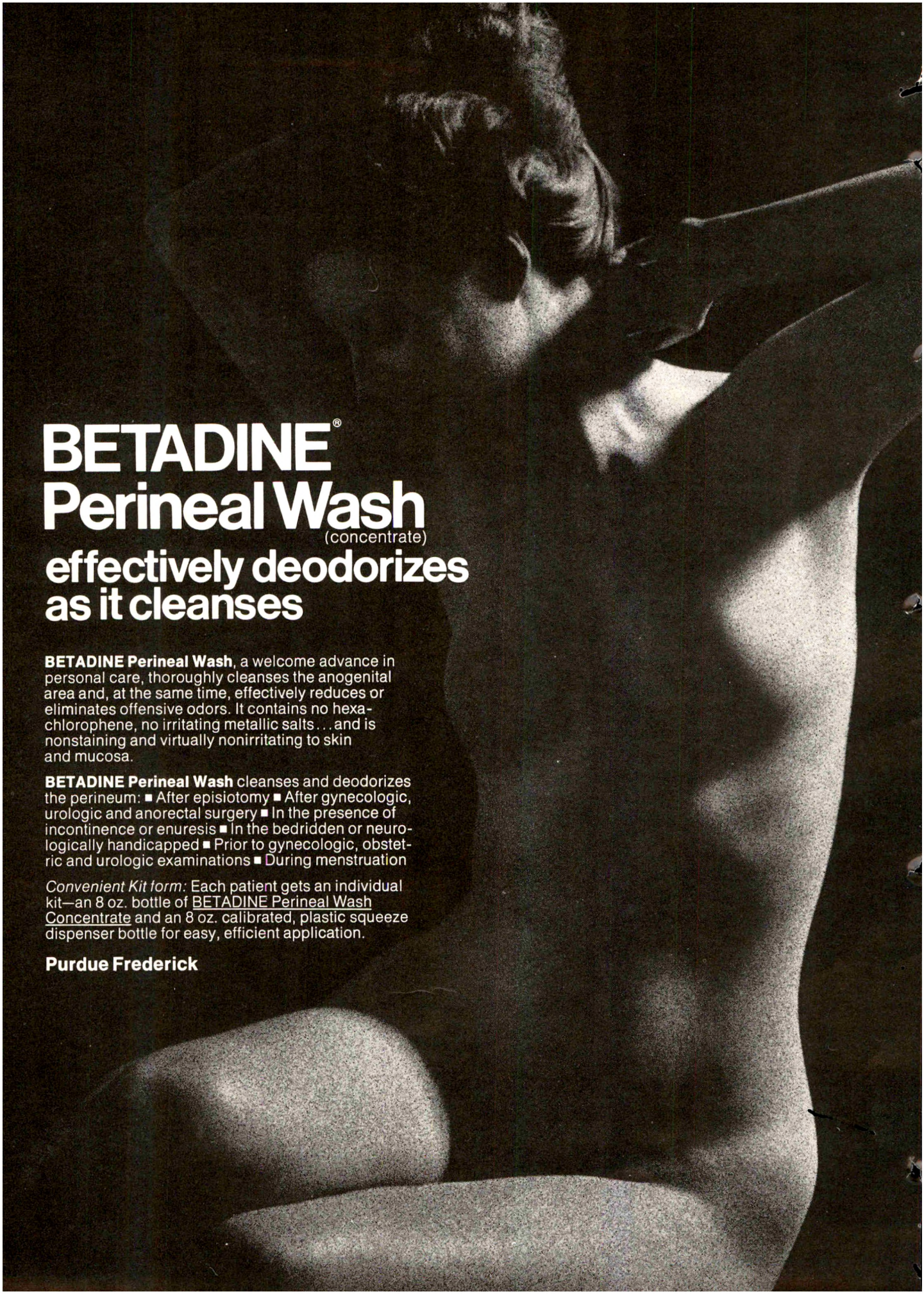
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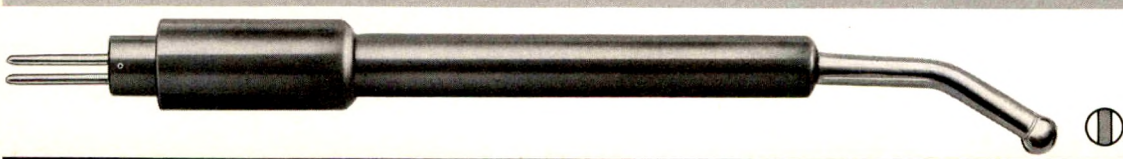
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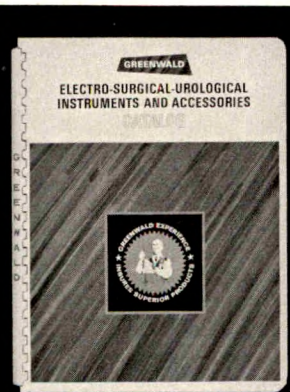
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1976, about 425 pp., in preparation
ISBN: 0-12-644450-1

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An International Journal

The Official Publication of the Society of Gynecologic Oncologists

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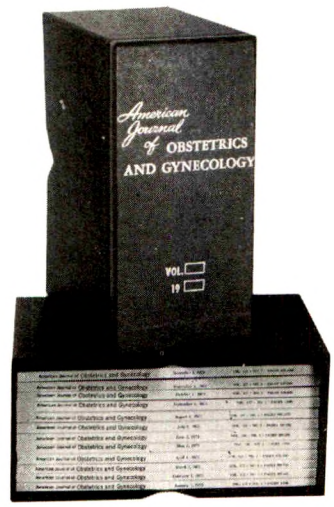
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Microbiologic aspects of fertility...

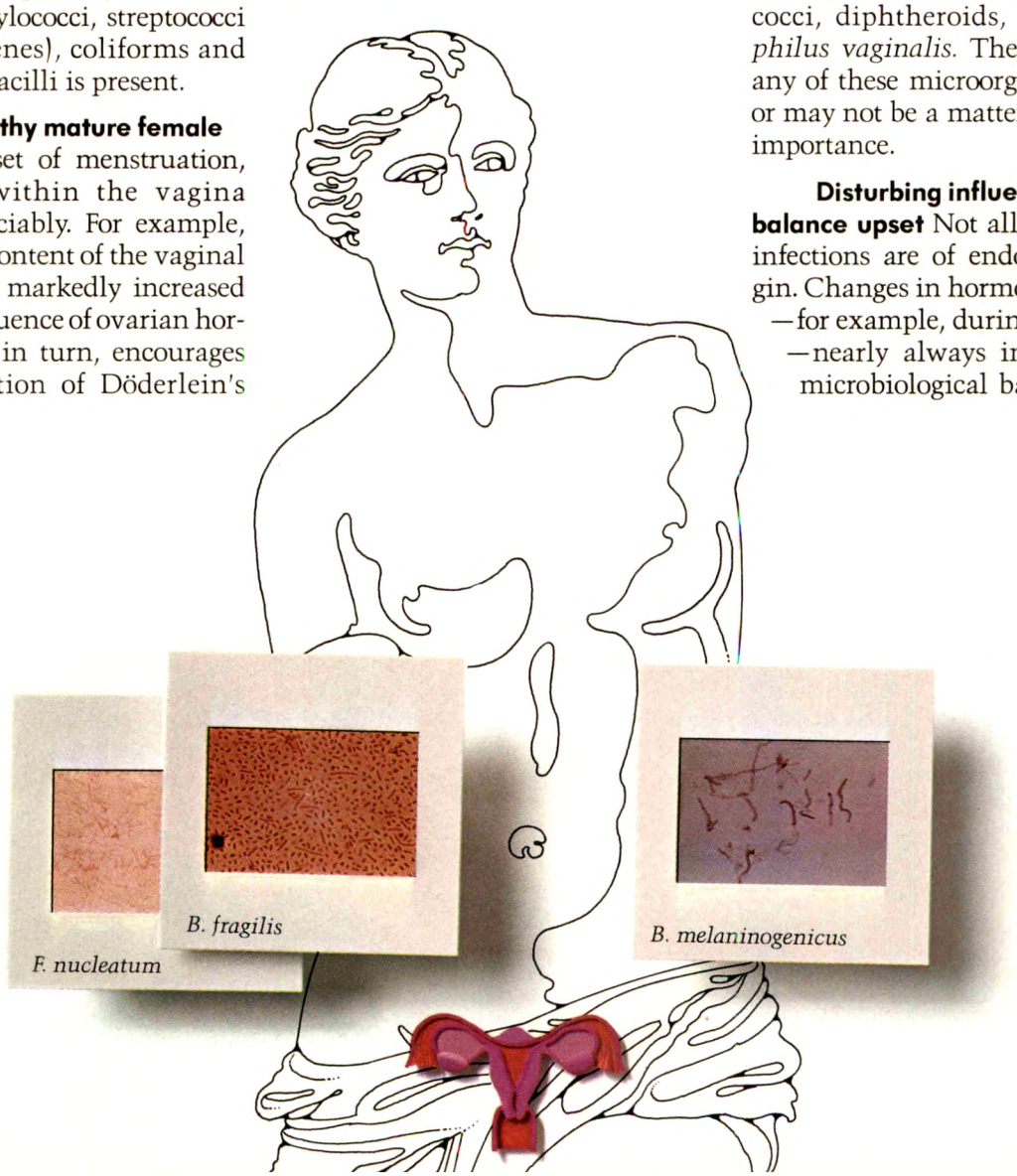
The greatest potential for bacterial infection in the female genital tract exists during the fertile years. A large proportion of the potentially pathogenic microflora are anaerobic—particularly bacteroides and anaerobic streptococci. Isolation and identification present special problems.

"Pseudo-maturity"
Sterile at the time of birth, the female genitalia begin to develop an abundant bacterial flora within hours. But this maternally influenced flora, composed largely of the familiar gram-positive lactobacillus known as Döderlein's bacillus, disappears in just a few weeks. The vaginal secretions revert toward alkalinity and remain alkaline until puberty. A varied flora of staphylococci, streptococci (except pyogenes), coliforms and diphtheroid bacilli is present.

The healthy mature female
With the onset of menstruation, conditions within the vagina change appreciably. For example, the glycogen content of the vaginal epithelium is markedly increased under the influence of ovarian hormones. This, in turn, encourages the proliferation of Döderlein's bacilli. These lactobacilli create an acid environment which limits the growth of potential pathogens, and the role of lactobacilli in keeping the microflora in balance is vital throughout a woman's reproductive years.

The normal flora—anaerobes predominate Certain other bacteria are also seen regularly in the vagina. With today's improved methods of culturing, it has been demonstrated that a large proportion of these bacteria are anaerobic—notably bacteroides and anaerobic streptococci. Other microorganisms that may be observed are the *Escherichia coli/Enterobacter aerogenes* group of coliforms, the anaerobic micrococci, group B streptococci, enterococci, diphtheroids, and *Hemophilus vaginalis.* The presence of any of these microorganisms may or may not be a matter of etiologic importance.

Disturbing influences—balance upset Not all gynecologic infections are of endogenous origin. Changes in hormonal balance—for example, during pregnancy—nearly always influence the microbiological balance. Both



the resident bacterial population and potential invading pathogens may be affected. Either may be responsible for the occurrence of postpartum infections, postabortal infections, posthysterectomy infections, and the infections that occur concurrently with neoplastic disease. As pathogens ascend the reproductive tract from vagina to uterus to tubes, the risk to the patient is usually enhanced.

Forms of infection

Gynecologists and surgeons alike are well acquainted with such infections: abscesses (whether tuboovarian, pelvic, vaginal, vulval, or Bartholin's gland infection), puerperal sepsis, salpingitis, endometritis, peritonitis of gynecologic origin, vaginal-cuff infection, chronic pelvic inflammatory disease—with each, the threat of possible septicemia. The need for immediate surgical intervention may be controversial, but certain of these infections often represent true gynecologic emergencies.

The problems anaerobes pose...culturing

Improved culturing techniques have demonstrated that anaerobes—especially bacteroides and anaerobic streptococci—inhabit the vagina, as well as more remote genital areas. It has been reported that these usually foul-odor-producing anaerobic organisms may be isolated in three out of four cases of infections of the genital tract. In one series of patients, anaerobes alone were cultured in 37 percent of the cases. Many studies have shown that bacteroides are by far the most common of these organisms, but anaerobes such as peptococci, peptostreptococci and other anaerobic streptococci are also frequently observed. Mixed infections with multiple anaerobic species are not unusual.

Today many physicians suspect that the techniques of obtaining or incubating the culture may be at fault if no anaerobes at all are observed.

A new appreciation of pathogenicity

Only recently has it been realized that anaerobes other than clostridia are pathogens of major significance in serious infections of the female genital tract. Exacting methods of culturing have helped to establish this. One investigation has shown that 44 percent of all anaerobic isolates obtained from a series of 400 patients of all types, not just gynecologic, were associated with infection. Bacteroides and anaerobic streptococci were the most prevalent, with clostridia occurring less frequently.

Whenever these organisms are seen on repeated occasions by Gram stain or isolated by culture—whether alone or combined with other bacteria—they should not be ignored.

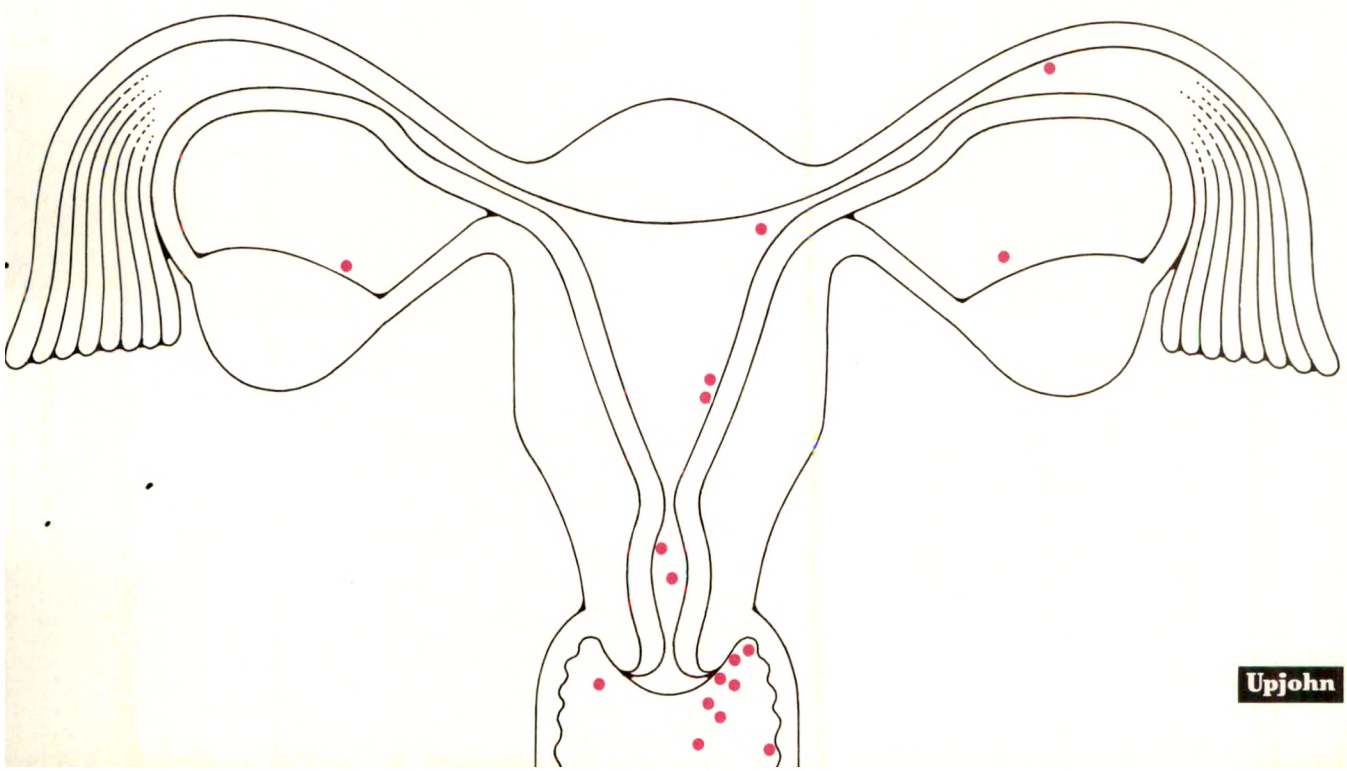
Therapeutic measures

Selection of the most appropriate antibiotic—or antibiotics—is still a problem for the gynecologist in many instances, since many of the infections he deals with cannot be etiologically defined when first observed. Nevertheless, the seriousness of his patient's condition may demand immediate attention. Because there are numerous antibiotics effective against just certain potential pathogens, the physician's problem has been intensified. And for one aspect of his problem—anaerobic infections—there has been no easy answer.

Many gynecologists believe that, of all infections, these present one of today's most serious challenges.

For information on ONE ANTIBIOTIC OF SIGNIFICANCE in the treatment of serious anaerobic infections of the female reproductive tract, please turn page.

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Therapeutic considerations...

Cleocin® Phosphate (clindamycin phosphate injection) has proved to be effective against susceptible anaerobic organisms (whether they are anaerobic cocci or anaerobic gram-positive or gram-negative rods). Specifically its activity has been established in serious infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal-cuff infection caused by susceptible strains of bacteroides, fusobacteria, peptococci, peptostreptococci, microaerophilic streptococci, or clostridia.* Furthermore, Cleocin PO_4 has proved successful in septicemia and in such nongynecologic conditions as serious intra-abdominal infections (peritonitis, intra-abdominal abscess), serious respiratory-tract infections (empyema, anaerobic pneumonitis, lung abscess), and serious infections of skin and soft-tissue caused by susceptible anaerobic organisms.

Since disc susceptibility testing with current methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility to clindamycin.

Also of value in serious gram-positive infections The use of Cleocin PO_4 in serious nongynecologic infections caused by susceptible gram-positive organisms has been extensively investigated both bacteriologically and clinically. Because Cleocin PO_4 is a parenteral antibiotic, emphasis has been on evaluation of the drug in serious infections, and the appropriate patients for Cleocin PO_4 are those who are hospitalized with serious illnesses.

Diagnoses have included septicemia and septic shock, acute peritonitis, staphylococcal pneumonia, and massive wound infection. In many cases the infection was secondary to severe accidental trauma, major surgery, or debilitating disease.

Cleocin PO_4 has produced excellent results when the pathogens in these serious infections proved to be staphylococci, streptococci (except enterococci), or pneumococci. With rare exceptions, the organisms proved susceptible *in vitro* and were successfully eradicated from the clinical lesions, regardless of the severity of the infection. Its use in these infections should be reserved for penicillin-allergic patients for whom, in the judgment of the physician, a penicillin is inappropriate.

Other therapeutic considerations:

1) Cleocin PO_4 is clinically effective in serious infections caused by penicillin-resistant or penicillinase-producing staphylococci. However, staphylococcal strains resistant to clindamycin have been encountered, and susceptibility testing should be performed.



2) Cleocin is useful in patients who are sensitive to penicillin. Rare cases of sensitivity to Cleocin resulting in maculopapular rash and urticaria have been reported; as with all antibiotics, it should be used cautiously in atopic patients. Serious anaphylactoid reactions require emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated. However, no actual cross-antigenicity with other antibiotics has been demonstrated, *except with lincomycin.*

Because of these two benefits, Cleocin PO_4 can fill a need both for penicillin-sensitive patients and those harboring penicillin-resistant organisms.

Cleocin PO_4 should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section of the brief summary on the following page.

WARNINGS: (See WARNING box on following page.)

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued. (See WARNING box and summary of prescribing information on following page.

Safety for use in pregnancy has not been established.

*Clostridia are more resistant than most anaerobes to clindamycin. Some species, e.g., *C. sporogenes* and *C. tertium*, are frequently resistant to clindamycin.

STERILE SOLUTION

...Cleocin® PO4

clindamycin phosphate injection, Upjohn

WARNING

Clindamycin can cause severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to . . . . . 150 mg clindamycin base

benzyl alcohol . . . . . 5 mg

disodium edetate . . . . . 0.5 mg

water for injection . . . . . qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: (See WARNING box.) Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.



Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of non-susceptible organisms, particularly yeast. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

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Cleocin PO4

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Premarketing clinical trials of LO/OVRAL showed a remarkably low incidence of breakthrough bleeding. Now, after almost twice the total cycles among 1633 women, the incidence of breakthrough bleeding† remains gratifyingly low—an average of only 3.0 percent in 20,312 total cycles.

Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment.* These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

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IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

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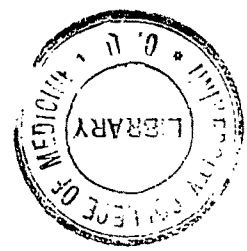
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OBSTETRICS

Oral prostaglandin E_2 for labor induction in high-risk pregnancy

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Oral prostaglandin E_2 (PGE_2) was used alone or synergistically with intravenous oxytocin to induce labor in 84 women whose pregnancies were at high risk. A control group of 84 similar high-risk pregnancies where labor was induced with intravenous oxytocin alone was studied to compare the safety and efficacy of the two regimens. Oral PGE_2 administration, combined with the synergistic effect of intravenous oxytocin, is safe for induction of labor in gravid women whose fetuses are at risk. Uterine polysystole, which is potentially dangerous, especially to the high-risk fetus, was not commonly encountered and only once was associated with transient fetal bradycardia. Uterine hypertonus was not encountered with PGE_2; however, it did occur with oxytocin stimulation. Nausea and vomiting occurred in one third of the women treated with PGE_2 but were well tolerated and required discontinuation of the drug in only one instance. There was no apparent advantage of using the combination PGE_2 regimen in patients whose cervices were more favorable for induction of labor (Bishop score, 5 to 9). However, oral PGE_2, used either alone or synergistically with oxytocin, appears twice as effective in inducing labor than was oxytocin alone in women in whom labor was considered to be "difficult to induce" (Bishop score, 0 to 4).

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SINCE KARIM'S[1] initial observation that orally administered prostaglandin E_2 (PGE_2) initiated labor in term human pregnancy, subsequent studies from the United Kingdom have affirmed its safety but have

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Table I. Primary and secondary indications for induction of labor in gravid women given oral PGE_2 or oxytocin (control group)

Primary indication	*PGE_2 (No. = 84) (%)*	*Control (No. = 84) (%)*	*Secondary indication**	*PGE_2*	*Control*
Pregnancy-induced hypertension	62	70	IUGR	9.6	5
			Postmaturity	9.6	6.8
			Diabetes	2	–
			SC hemoglobin	–	1.7
Chronic hypertension with pregnancy aggravation	17	13	IUGR	38.5	9
			Postmaturity	–	9
			Diabetes	–	9
			Renal disease	7	–
Postmaturity	9	10.7	IUGR	–	22
			SC hemoglobin	12.5	
Fetal growth retardation (IUGR, dysmaturity)	6	3.6			
Diabetes (Class B)	5	2.4			
RH_0 isoimmunization	1				

IUGR = Intrauterine growth retardation.

*Expressed as per cent of primary indication.

yielded varied success rates.[2–7] In these studies, there was no uniform dose employed and there were wide variations of total dose administered. Moreover, the time interval between doses as well as the total time of drug administration varied. In addition, amniotomy was performed prior to administration of the drug in two of these studies.[5, 6] Some women with "high-risk pregnancies" were included in these as well as other studies, and it was concluded that PGE_2 could be administered safely to these women.[4, 6–10]

In the United States, the first studies performed with oral PGE_2 involved normal healthy gravid women at term whose cervices were favorable for "elective induction of labor."[11, 12] Lauersen and Wilson[13] subsequently reported that orally administered PGE_2 was both safe and effective in 52 women, approximately three fourths of whom could be considered as women whose fetuses were at risk.

Elective inductions of labor for convenience are not performed at Parkland Memorial Hospital. However, induction is frequently required for either pregnancy-related or other complications that demand delivery. The cervix in these women is frequently "unfavorable," and induction of labor is judged likely to be difficult. For these reasons, the present study was designed to evaluate the safety and efficacy of of oral PGE_2 in inducing labor in high-risk obstetric patients, i.e., in pregnant women whose fetus is considered at risk. If PGE_2 administration alone was found to be ineffective in labor induction, it was planned to assess the "synergistic" effect of oxytocin that allegedly follows PGE_2 administration to term pregnant women as noted by Barr and Naismith.[3, 4] In order to analyze the efficacy and safety of this "combined" regimen, a similar group of patients who received only intravenous oxytocin was studied, and the results obtained in the two groups were compared.

Material and methods

Patients. Eighty-four patients were given oral PGE_2 alone or PGE_2 followed immediately by oxytocin, for a total of 95 times. The control group of 84 patients received only intravenous oxytocin for a total of 133 times. Some of the women who were not delivered during the study period were given uterotonic agents at times remote from the study periods. The outcome of these labor inductions are not considered in the comparative results. All women had pregnancies classified as "high risk," and at the time of the study induction(s) it was judged that delivery was indicated for these complications. In women receiving the investigational drug, informed consent by written notification was obtained. The majority of patients of both groups had been hospitalized on the High Risk Pregnancy Unit of Parkland Memorial Hospital.

The most common indication for induction of labor in this study was one of the hypertensive disorders of pregnancy, either pregnancy-induced hypertension or chronic hypertension with superimposed pregnancy-aggravated hypertension (Table I). Other than premature rupture of the fetal membranes, these hypertensive conditions constitute the most common indications for induction of labor at Parkland Memorial Hospital. The results in patients with premature rupture of the membranes, often otherwise normal, are not included in this study but will be described in a future report.[14]

Table II. Comparison of mean values for four factors in two groups of gravid women in whom labor was induced with oral PGE_2 or oxytocin (control group)

	All patients		*Bishop score 0-4*		*Bishop score 5-9*	
Factor	*PGE_2 (No. = 84)*	*Control (No. = 84)*	*PGE_2 (No. = 49)*	*Control (No. = 47)*	*PGE_2 (No. = 35)*	*Control (No. = 37)*
Maternal age	21.5	21.1	22.0	21.6	20.8	20.4
Parity	0.64	0.57	0.71	0.64	0.54	0.48
Gestational age	39.4	39.2	38.9	39.0	40.1	39.5
Bishop score	4.13	4.24	2.79	2.58	6.0	6.35

All pregnancies judged to be postmature had exceeded the forty-second week of gestation on the basis of several criteria that included: (1) an accurate last menstrual period confirmed by early examination, (2) quickening that coincided with the last menstrual period, and/or (3) an examination at which time the uterus was palpated at the umbilicus and fetal heart tones were first heard with a standard fetoscope. Confirmation of cessation of fetal growth was obtained in the majority of these cases by serial ultrasonography.

The clinical impression of fetal growth retardation (intrauterine growth retardation, fetal dysmaturity) was usually demonstrated by the lack of maternal weight gain and/or lack of fetal growth. These impressions were also confirmed by serial sonographic measurements. In all cases the diagnosis was substantiated by the examination of the newborn infant by an experienced neonatologist. This syndrome, i.e., intrauterine growth retardation, occurred more commonly in patients with one of the hypertensive disorders; however, this diagnosis was also reached in eight otherwise normal women (Table I).

Women in the control group, i.e., those who received only oxytocin for labor induction, were chosen from both prospective and retrospective analyses. All patients selected retrospectively had been hospitalized for variable periods of time on the High Risk Pregnancy Unit. The control group was matched with the study group for parity, gestational age, inducibility rating by Bishop's score,[15] and to some extent by maternal age. These two groups are very similar (Table II).

Drug. Oral prostaglandin E_2 tablets (U-12,062) containing 0.5 mg. of the active drug were supplied by The Upjohn Co. The Upjohn Co. Protocol No. 7027 dose schedule was used: After an initial observation period during which time uterine activity was found to be absent, by both clinical and electronic monitoring, an initial dose of 0.5 mg. of PGE_2 was given, but the dose was increased by 0.5 mg. hourly if satisfactory uterine activity had not commenced. In no case did a single dose exceed three tablets (1.5 mg).

Usually the drug was given hourly, even if adequate contractile uterine activity was considered to exist. However, occasionally a dose was omitted if uterine polysystole developed. Throughout the induction period, each patient was monitored continuously, by both clinical and electronic means.* External electronic monitoring was used prior to rupture of the fetal membranes. Following rupture of the membranes, a fetal scalp electrode was placed, usually in combination with an intrauterine pressure catheter.

Except when evidence of fetal distress dictated abandonment of the protocol and abdominal delivery, PGE_2 was given for at least eight hours. After this time the drug was continued if labor was progressing. If progress had ceased, PGE_2 was discontinued. At this time, intravenous oxytocin was begun within two hours, or the induction was stopped. If the latter was chosen, the woman was returned to her room or abdominal delivery was carried out, depending on the clinical criteria of each case. In the control group, each induction was performed by the intravenous infusion of oxytocin at a determined rate with the use of an infusion pump for a minimum of eight hours. The incremental dose of oxytocin was increased each 15 to 30 minutes, depending on the uterine response.

Amniotomy. The timing of rupture of the membranes, whether spontaneously or by amniotomy, varied, but there was a tendency to perform amniotomy earlier in the active phase of labor in the PGE_2 group. Moreover, amniotomy was performed more commonly in the study group during the latent phase of labor when cervical changes were occurring with good contractions by clinical estimation. A similar number of patients in each group had amniotomy performed in the latent phase, during which no cervical change had occurred but good contractions were clinically apparent. Only one patient in the PGE_2 group and three in the control group had amniotomy when no uterine contractions were detectable. Eigh-

*Model 101B, Corometrics Medical Systems, Inc., 2 Barnes Industrial Park Rd., Wallingford, Connecticut 06492.

Table III. Outcome of induction(s) performed in 84 patients in whom PGE_2 with or without combined oxytocin was used compared to 84 women in whom labor was induced with oxytocin only (control group). Note number of patients listed under "cesarean section" in whom active labor was induced

Outcome of delivery	*PGE_2 group (No. = 84)*	*Control group (No. = 84)*
Vaginal delivery		
PGE_2 alone	21	
PGE_2 + oxytocin	27	48 (57.1%)
Oxytocin alone		39 (46.4%)
Cesarean section		
PGE_2 alone	12	
PGE_2 + oxytocin	12	24 (28.6%)
Oxytocin alone		20 (23.8%)
Fetal distress	8*	1
Failure of labor to progress	6	10
Poor contractions	5	7
Cephalopelvic disproportion	5	2
	14/24 active labor	5/20 active labor
Failure to deliver		
PGE_2 alone	9	
PGE_2 + oxytocin	3	12 (14.3%)
Oxytocin		25† (29.8%)

*Two patients received oxytocin. One patient had prolapse of the cord. (See text.)

†Fifteen had two or more inductions.

teen PGE_2 patients and 22 control patients had no amniotomy during the final study induction.

Clinical and laboratory monitoring. Blood pressure, pulse, and temperature were determined at half-hour intervals. Preinduction laboratory tests included hemoglobin and hematocrit, white blood cell count with differential determination, serum creatinine, serum glutamic oxalacetic transaminase, uric acid, and alkaline phosphatase. These tests were repeated within 24 hours following delivery or after discontinuation of the experimental drug if delivery did not occur.

Results

The purpose of this study was to evaluate the safety and efficacy of PGE_2 used alone or synergistically with oxytocin for inducing active labor. Therefore, the success rate was analyzed in terms of both safety and resultant vaginal delivery. The two study groups were compared, then subdivided, and analyzed according to: (1) inducibility rating (Bishop score), and (2) parity plus inducibility rating.

Analysis of success in over-all group.

Vaginal deliveries. The success rate of effecting vaginal delivery with PGE_2 used alone or in combination with oxytocin was 51.7 per cent compared to a success rate of 46.4 per cent in the group in whom oxytocin alone was used. This difference is not significant (Table III).

Cesarean sections. The patients considered in this category are those who were delivered by cesarean section during the induction period. Four subcategories are defined: (1) fetal distress—fetal bradycardia, detected clinically or by electronical monitoring, significant enough to warrant immediate delivery; (2) failure of labor to progress—cessation of cervical dilatation despite apparently adequate uterine contractions; (3) poor contractions—absence of apparently adequate clinical contractions during the induction period; and (4) cephalopelvic disproportion—failure of the presenting part to descend after the active phase of labor began.

In the PGE_2 group, 28.6 per cent of the 84 patients underwent cesarean section during the attempt at induction (Table III). Half of these patients had received oxytocin following discontinuation of PGE_2. In the control group, 23.8 per cent of the women were delivered by cesarean section. These 20 patients had a total of 44 inductions of labor with oxytocin. Eight infants in the PGE_2 Group were delivered abdominally because of fetal distress; however, two of the mothers were receiving oxytocin at the time fetal distress was detected. A third infant was delivered because of prolapse of the umbilical cord when the cervix was dilated 3 cm.

Failure to deliver. These women received a minimum of eight hours of trial to induce labor with either drug regimen, and either they had no clinical contractions or the contractions were insufficient enough to produce cervical dilatation. Uterotonic agents were discontinued, and the patients were returned to their rooms; immediate abdominal delivery was not warranted.

As previously stated, the success of either drug

Table IV. Ultimate outcome of patients in both groups classified as "failures to deliver." Half of patients in each group ultimately underwent cesarean section to accomplish delivery

Outcome	*PGE_2 group (No. = 12)*	*Control group (No. = 25)*
Spontaneous labor		
Vaginal delivery	3	10
Cesarean section	2	2
	5	12
Induction of labor		
Vaginal delivery	3	3
Cesarean section	3	6
	6	9
Elective cesarean section	1	4
Total		
Subsequent vaginal delivery	6	13
Subsequent cesarean section	6	12

regimen was judged by its ability to initiate active labor. Of the 24 patients in the PGE_2 group who were delivered abdominally, 14 were adjudged to be in the active phase of labor at the time of cesarean section. Contrariwise, only five of the 20 patients in the control group undergoing cesarean section during the study period were considered to be in active labor. Therefore, the success rate of *inducing labor* for the PGE_2 Group was 73.8 per cent. In the control group, only 52.4 per cent of the women had active labor initiated by oxytocin during the trial period. This higher success rate for the experimental drug regimen is significant ($p < 0.01$) by the chi-square method in a 2 by 2 contingency table.[16]

The rate of failure to deliver either vaginally or by cesarean section during the induction period was twice as great in the control group compared to the PGE_2 group (29.8 versus 14.3 per cent). Thirteen of the 25 "failures" in the control group were among women treated on two successive days and two women treated for three successive days. The subsequent fate of the 37 women in both groups who failed to deliver during the study induction(s) is presented in Table IV. In each group, half of these women ultimately underwent cesarean section for a variety of reasons.

Analysis by cervical status and parity.

Bishop score 0 to 4. Active labor was successfully induced in 71.4 per cent of the PGE_2 group with a Bishop score of 0 to 4 compared to 35.5 per cent of women in the control group (Fig. 1). This difference is significant ($p < 0.01$).

Labor was successfully induced in 64.7 per cent of nulliparous patients with a Bishop score of 0 to 4 in the PGE_2 group. Oxytocin alone was successful in initiating active labor in only 33.3 per cent of the control group. This difference is statistically significant, ($p < 0.05$) (Fig. 1).

Active labor was induced in 86.7 per cent of the multiparous patients in the PGE_2 group with a Bishop score of 0 to 4 compared to only 41.7 per cent of women in the control group (Fig. 1). The difference is also significant ($p < 0.02$) according to the Fisher Exact Probability Test.[16]

Bishop score 5 to 9. The active phase of labor was induced in a similar number of patients in each group whose Bishop scores were 5 to 9 (Fig. 2). Likewise, the number of vaginal deliveries, cesarean sections, and "failures" were comparable in these women. Analysis of nulliparous and multiparous patients in this subcategory also demonstrated no difference in success rates with either drug regimen.

Neonatal outcome. All infants were discharged from the hospital in good health. Three of 72 infants delivered in the study group (4 per cent) had five-minute Apgar scores of less than 7. In one infant with an Apgar score of 6/6, the low score was attributed to delay in delivery following general anesthesia for cesarean section. A second infant (Apgar score, 1/3) was "depressed" following vaginal delivery and developed bilateral pneumothoraces but ultimately did well. The third infant (Apgar score, 6/6) was delivered after a long labor following 19 hours of oxytocin stimulation that followed PGE_2 administration.

Six of 59 infants in the control group (10 per cent) delivered during the induction had five-minute Apgar scores of less than 7. Three of these infants were delivered by cesarean section. Two others had meconium staining of the amnionic fluid, and the sixth was growth retarded.

One neonatal death occurred. An infant in the study

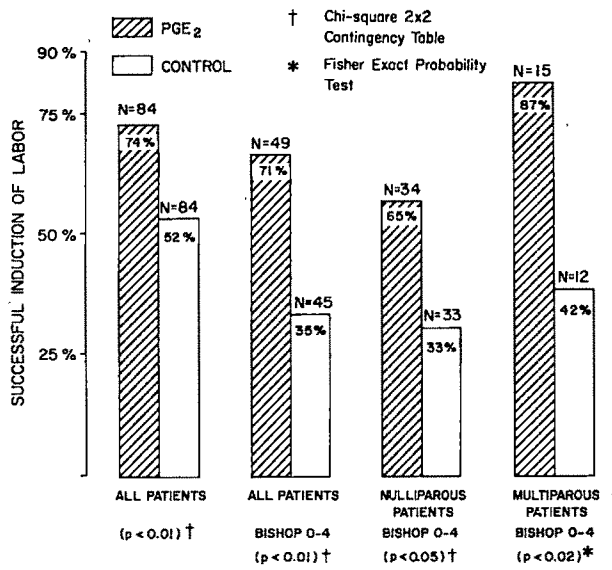


Fig. 1. Comparison of success rates for the induction of labor in women with low (0 to 4) Bishop scores. The women who received PGE_2 with or without oxytocin (PGE_2) are compared with the 84 patients who received only oxytocin (control). Each group is analyzed for successful induction of labor in patients with Bishop scores of 0 to 4 as well as for parity combined with Bishop scores of 0 to 4.

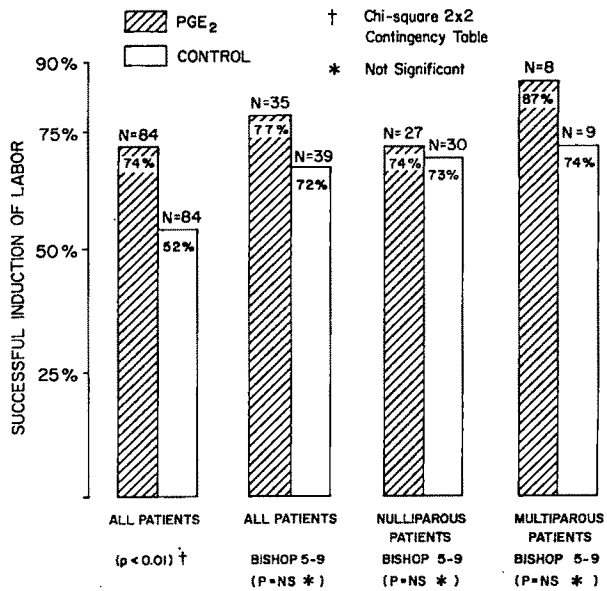


Fig. 2. Comparison of success rate for the induction of labor in two groups of women with cervices more favorable for induction (Bishop scores 5 to 9). Women in both over-all groups are compared to all patients with Bishop scores of 5 to 9 and analyzed for parity as well.

group died at home suddenly on the fourteenth day. A severe congenital heart defect was demonstrated by autopsy examination.

Side effects.

Polysystole and hypertonus. In three of the 95 patients given PGE_2, polysystole (defined as more than five contractions per 10 minutes) developed. In one, a grand multipara, transient fetal bradycardia developed but resolved spontaneously in 10 minutes. After a rapid labor, she was delivered of a healthy infant (Apgar score, 8/9) 30 minutes later. A second patient had 5 or 6 "hard contractions" each 10 minutes for six continuous hours without apparent adverse effects. The third patient had 5 to 7 contractions per 10 minutes for seven hours, also without apparent adverse fetal effects. These three patients developed polysystole while receiving the smallest dose of the drug. In the latter two patients, polysystole persisted for several hours after the drug was discontinued, suggesting that either an intrinsic mechanism was operative or the drug effect was prolonged.

Another patient in the study group developed polysystole while receiving oxytocin, the last dose of PGE_2 having been given six hours earlier. The polysystole resolved after the oxytocin infusion was stopped.

No instance of base-line hypertonus was observed with PGE_2. In one patient in whom PGE_2 had been discontinued, a base-line uterine tonus of 25 to 40 mm. Hg developed after 12 hours of oxytocin administration. The hypertonus resolved following cessation of the oxytocin infusion.

Vomiting and diarrhea. Mild to moderate emesis occurred in 35 per cent of patients given PGE_2. This was not necessarily dose related; however, if vomiting occurred with the 0.5 mg. dose, it could be predicted that a larger dose would also provoke emesis. In one woman, the second induction with PGE_2 was accompanied by severe emesis with the 0.5 mg. dosage, and delivery was accomplished by cesarean section because of no uterine activity.

Diarrhea occurred in three patients but was not severe.

Blood pressure. A computer analysis of systolic and diastolic blood pressures taken twice an hour during the induction period was performed. No significant change in blood pressure occurred during administration of PGE_2.

Laboratory tests. No abnormalities in hematologic or biochemical tests were found from an analysis of these studies performed before and after PGE_2 administration.

Comment

In 1971, Karim and Sharma[2, 17] indicated that prostaglandins $F_{2\alpha}$ and E_2, given either intravenously or orally, were virtually 100 per cent effective in inducing labor and delivery in the gravid woman at term. This high success rate for oral prostaglandin E_2 was not subsequently reaffirmed by European investigators who reported success rates of 64 to 92 per cent.[3–6] Two studies were reported in which oral PGE_2 was compared with intravenous oxytocin. Almost identical success rates were found with either drug used for inducing labor.[8, 18]

Undoubtedly, many factors influence the success rate of labor induction with any uterotonic agent. These include parity and gestational age, but the most important factor likely is the "inducibility of the cervix." This latter factor, for purposes of data analysis, is usually evaluated and assigned a numerical score according to Bishop's criteria.[15]

In the present study with the use of oral PGE_2 synergistically with oxytocin, we observed a success rate of 73.8 per cent in inducing labor in high-risk patients. In the control group (oxytocin only), labor was successfully induced in only 52.4 per cent of the patients. Although this difference is statistically significant, the data are more impressive when only patients with low Bishop scores are compared. In the experience of most investigators, the highest number of failures occur in these patients. The majority of our patients (58 per cent) had Bishop scores of 0 to 4. This explains, in part, our lower success rate for labor induction with PGE_2 compared to Lauersen and Wilson's 98 per cent success rate in a group of high-risk patients.[13] Of their 52 patients, 35 per cent had Bishop scores of 0 to 3.

The nulliparous state confers more difficulty in labor induction. In this series, 73 per cent of the patients were nulliparous, whereas only 40 per cent of Lauersen and Wilson's patients were nulliparous.[13] Similarly, in Karim and Sharma's group of 764 women, only 23 per cent of patients were having their first delivery.[7] From our results with nulliparous patients with a low Bishop score (0 to 4), it was demonstrated that PGE_2 in combination with oxytocin is significantly more effective in inducing labor than when oxytocin is given alone.

When the efficacy of PGE_2 in successfully inducing labor is considered, an important factor is the total single dose of drug given as well as the length of time administered. Individual doses of PGE_2 up to 3.0 mg.[6, 13, 18] have been administered as often as every half hour.[13, 18] Indeed, Karim and Sharma[7] have given as much as 2 mg. every two hours for as long as 48 hours. These larger single doses given at shorter time intervals for longer times may also account, in part, for the higher success rates reported by other investigators.

Amniotomy and its timing must also be considered in ascertaining the efficacy of a drug regimen in inducing labor, even though its exact effect remains unknown. This may be especially true in those patients in whom the cervix is less favorable for induction. In this study, amniotomy was performed at comparable times in the patients of each group. Therefore, it is believed that the effect of this variable was negated. For example, 30 per cent of the patients in both groups sustained "early amniotomy," i.e., when contractions were occurring but at a time before the active phase of labor began.

In 1972, Barr[3] noted a "synergistic" effect of oxytocin on the term uterus following administration of oral PGE_2; however, Friedman and Sachtleben[19] concluded that preinduction "priming" with PGE_2 did not enhance the efficacy of intravenous oxytocin. Our experimental design was formulated to allow an evaluation of the enhanced or synergistic effect of oxytocin following E_2 administration. Our results support Barr's contention that "synergism" does indeed exist; moreover, this enhanced effect in the induction of labor is more evident in the patient with an unfavorable cervix. In the women with a more favorable cervix, there appears to be no advantage in using PGE_2 rather than intravenous oxytocin.

To our knowledge, this is the first study of labor induction by PGE_2 that dealt only with high-risk pregnancies. The results of this study substantiate the safety of this drug in these women and their fetuses. The relatively high frequency of fetal distress encountered is a reflection of the high-risk gestations under study. The rate of abdominal delivery, approximately one third in both groups, is not exceedingly high for a group of such patients. Cooper and colleagues[20] have reported a 28 per cent cesarean section rate for a similar group of 89 pregnancies.[20]

In summary, from the results of this study we conclude that PGE_2 used alone or synergistically with intravenous oxytocin is superior to oxytocin alone in inducing labor in women whose fetus is at risk and in whom the cervix is considered unfavorable for labor induction.

In most cases, amniotomy was performed only after the onset of good uterine contractions by clinical criteria and usually after the active phase of labor began.

The higher success rate of inducing active labor with

PGE_2 used alone or followed by oxytocin, compared to oxytocin alone, is more impressive in patients in whom the cervix is unfavorable for induction (Bishop score, 0 to 4). In all patients with a Bishop score of 0 to 4, irrespective of parity, the PGE_2 regimen was twice as effective in inducing labor than was oxytocin alone. This increased efficiency also obtains in patients with low Bishop scores, whether they are nulliparous or multiparous. There is no apparent advantage of using oral prostaglandin E_2 over oxytocin alone in patients with higher Bishop scores.

Potentially dangerous side effects such as uterine polysystole were encountered uncommonly. In only one case was polysystole associated with fetal bradycardia, and this was transient. This patient had a precipitate labor but was delivered of a healthy infant. Uterine hypertonus was not encountered with PGE_2. Contrariwise, we have observed that oxytocin infused injudiciously may be accompanied by both hypertonus and fetal distress. It was demonstrated that no significant change in blood pressure occurred in patients receiving PGE_2 in either hypertensive or normotensive women. Less serious side effects, i.e., nausea, vomiting, and diarrhea, occurred in one third of patients receiving PGE_2; however, these side effects were usually not severe and in only one instance necessitated discontinuation of the drug.

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An analysis of the utility of plasma immunoreactive estrogen measurements in determining delivery time of gravidas with a fetus considered at high risk

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Although maternal estrogen excretion and plasma estrogen levels are widely used to assess fetal health, the utility of these tests in lowering perinatal mortality rates has not been established. In order to ascertain if, with the help of plasma immunoreactive estrogen measurements, a reduction in perinatal deaths could be achieved, a population of women with a fetus at high risk were randomly divided into two groups and studied prospectively: in 315 gravidas, the estrogen results were reported (Group A); in 307, they were not reported (Group B). Nine perinatal deaths occurred in Group A, 10 in Group B. Ten Group B women whose infant ultimately did well would have been delivered 28 days or more prematurely if management had been based solely on the basis of abnormal immunoreactive estrogen levels. Measurement of estrogen levels is of little value in management of women with a fetus at risk; it may even lead to erroneous premature delivery.

A VOLUMINOUS literature concerning estrogen production during pregnancy has accumulated since Zondek and Goldberg,[1] Greene and Touchstone,[2] and Frandsen and Stakemann[3] suggested that the evaluation of maternal estrogen excretion rates could serve as an indicator of placental function and fetal health or distress.

With refinement in methods, the estimation of total urinary estrogens was replaced by the measurement of urinary estriol. More recently, it has become possible to accurately measure estrogens in the plasma of pregnant women,[4-7] and many laboratories have employed these techniques to circumvent the problems associated with the accurate and complete collection and processing of 24 hour urine specimens.[8-11]

A large number of institutions have developed patient management protocols that are based, in part, on the results of estrogen assays. However, proof is lacking that the proposed benefits of patient management based on an evaluation of plasma estrogen levels or urinary estrogen excretion, i.e., a reduction in fetal and neonatal deaths, outweigh the possible harm: an increase in neonatal deaths resulting from inappropriate premature delivery. Indeed, the possibility of erroneously effecting the delivery of a premature infant as the result of management based on estrogen values is rarely mentioned or considered critically.

This controlled, prospective study was undertaken to ascertain (1) if, through the use of plasma immunoreactive estrogen measurements, perinatal mortality rates can be reduced; (2) if knowledge of plasma estrogen levels is advantageous in detecting those fetuses in distress when close clinical observation does not allow this diagnosis; (3) if patient management can be altered favorably irrespective of pulmonary maturity and gestational age, even if plasma estrogens may indicate a compromised fetus.

The results of this study are consistent with the view

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Table I. Mean values, standard deviations, and coefficients of correlation for eight replicate plasma immunoreactive estrogen measurements at various levels

Mean (ng./ml.)	*Standard deviation*	*Coefficient of variation (%)*
12	1.6	13.3
41	2.7	6.6
162	12.0	7.4
379	5.7	1.5
438	5.7	1.3

Table II. Indications for monitoring of estrogen levels

	Group A	*Group B*
Hypertensive disorders	210	203
Diabetes mellitus	27	24
Suspected fetal growth retardation	24	21
History of fetal wastage	3	4
Postmaturity	2	2
Others	49	53

Table III. Incidence of spontaneously occurring labor and of medically and surgically induced delivery

	Group A patients		*Group B patients*	
	No.	*%*	*No.*	*%*
Spontaneous labor or premature rupture of membranes	174	55.2	165	53.7
Primary induction of labor	80	25.4	95	30.9
Primary cesarean section	61	19.4	47	15.3

Table IV. Perinatal deaths*

	Group A	*Group B*
Stillbirths	4	7
neonatal deaths	5	3
Total	9	10

*More detailed description of the 19 perinatal deaths in Tables V and VI.

that the measurement of immunoreactive estrogen in the gravida whose fetus is considered at risk is of little or no utility in the management of such women.

Material and methods

The pregnant women included in the present study either attended the Obstetrical Complications Clinic or were hospitalized in the High-Risk Obstetric Unit of Parkland Memorial Hospital. The patients were randomly assigned to one of two groups: Group A (reported group) included those women whose hospital record number ended with 0 to 4. Group B (not reported group) was composed of patients who had a hospital record number ending with 5 to 9. The hospital numbers were assigned to each woman by administrative personnel before admission to the clinic or hospital.

In Group A, the plasma estrogen levels were measured and the results were reported promptly to the responsible physicians. Special notice was given to a physician if the plasma estrogen levels were consistently low or suddenly decreased. Prompt delivery was advised if a fall in concentration of plasma estrogens of more than 40 per cent from previous values occurred and was confirmed in a subsequent sample. Delivery was also urged in the gravida in whom multiple plasma samples contained less than 20 ng. per milliliter after 34 weeks' gestation. Not in all instances, fortunately, was the recommendation to effect delivery carried out, e.g., patients who did well clinically and had an abnormal immunoreactive estrogen level as the only significant finding were, as a rule, not delivered at that time.

In Group B women immunoreactive estrogen levels were measured, but the values were neither computed nor reported; they were computed and evaluated retrospectively.

Blood samples were obtained between 09:00 and 11:00 at each clinic visit for outpatients and twice weekly between 06:00 and 07:00 for patients hospitalized in the High-Risk Obstetric Unit. Only those women in whom three or more plasma estrogen determinations were available, the final sample within 1 week of delivery, are included in this report.

A total of 4, 678 plasma samples were assayed in the 622 women of this report, an average of 7.5 samples per woman. There were 315 gravidas in Group A and 307 in Group B.

Other methods utilized during the study period in the management of women with a fetus at high risk included frequent clinical examinations in all patients, serial sonography, analysis of the L/S ratio in amnionic fluid and creatinine clearance tests according to specific patient need.

Plasma immunoreactive estrogen levels were assayed by the method of Gurpide and associates.[5] Precision, accuracy, and specificity of this method have been discussed by these authors. The coefficients of varia-

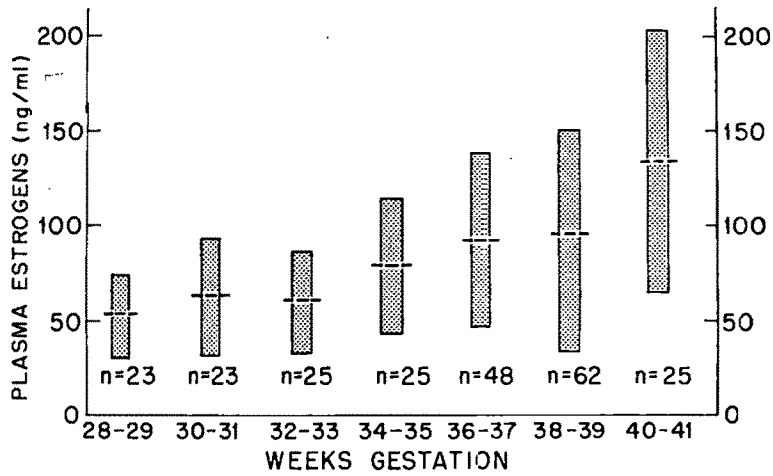


Fig. 1. Plasma estrogen levels in normal gravidas with mean ± 1 standard deviation.

tion of five samples with various estrogen levels measured in our laboratory, together with the means and standard deviations, are presented in Table I.

The mean plasma estrogen levels for 71 pregnant women between 28 and 40 weeks' gestation, together with one standard deviation, are illustrated in Fig. 1. Each of these women had well-dated, uncomplicated pregnancies terminating with the delivery of healthy, mature, appropriate-for-gestational age neonates.

Results

The maternal indications for monitoring estrogen levels in Groups A and B women are presented in Table II.

The mechanism of effecting delivery for the patients in each group is presented in Table III. In the majority of cases in both groups, labor began spontaneously or was induced following premature rupture of the membranes. While primary induction of labor was performed more often in Group B than in Group A, primary cesarean section was carried out more often in Group A than in Group B. In sixteen cases of Group A, the results of immunoreactive estrogen measurements influenced the decision to effect delivery. It could not be ascertained in how many cases normal estrogen levels contributed to a physician's decision to allow a pregnancy to progress; however, delivery was elective in a similar number of women in both groups.

A total of 19 perinatal deaths occurred (Table IV), resulting in a perinatal mortality rate for these high-risk pregnancies of 30.5 per 1,000 live births weighing 500 grams or more. The over-all perinatal mortality rate at Parkland Memorial Hospital during the period of study was 28.5 per 1,000 live births for all newborn infants weighing 500 grams or more.

In Table V the perinatal deaths of Group A and in Table VI, those of Group B are summarized. The patterns of immunoreactive estrogen levels for the individual cases of Group A and B are illustrated in Figs. 2 and 3, respectively.

The immunoreactive estrogen patterns in all pregnancies were studied: normal patterns occurred in 263 patients of Group A and 254 patients of Group B: the perinatal mortality rates were 15.2 and 19.7 per 1,000 live births for the groups, respectively. On the other hand, among cases with abnormal estrogen patterns—52 in Group A and 53 in Group B—five deaths occurred in each group, resulting in a perinatal mortality rate of 96 per 1,000 for Group A and 94 per 1,000 for Group B. In order to ascertain if close adherence to the patient management protocol could conceivably have prevented any of the perinatal losses, each case of perinatal death in both groups was analyzed separately. No perinatal loss could have been prevented with the appropriate utilization of serial plasma estrogens in Group A since all perinatal deaths were associated either with serious congenital malformations, with normal estrogen levels in twin gestation, or with abnormal estrogen levels which were not known until the mother went into labor (Table V).

The outcome of Cases Nos. 1 to 7 of Group B (Table VI) would also not have been influenced if estrogen levels had been reported for similar reasons. In three cases of Group B, though (Table VI and Fig. 3; Cases Nos. 8, 9, and 10), there may be grounds for arguing that the timely and proper interpretation of estrogen levels may have prevented perinatal death. These three cases are presented in detail.

Case reports

Case 8. A 38-year-old black woman, gravida 4, para 3, had had normal previous pregnancies, deliveries,

Table V. Perinatal deaths, Group A

Case No.	*Age*	*Gravidity parity*	*Indication for monitoring*	*Termination of pregnancy*	*Outcome*	*Estrogens*
1	21	3/2	Chronic hypertension	Spontaneous labor	2, 830 grams, Apgar 1/2, hypoplastic lungs—diaphragmatic hernia, neonatal death at 24 hr. of life	Normal
2	17	1/0	Severe pre-eclampsia	Oxytocin induction	1,120 grams, stillborn, anencephaly	Low, consistent with anencephaly
3	18	1/0	Pre-eclampsia	Oxytocin induction	3,000 grams, Apgar 6/9, Fallot's tetralogy, neonatal death on day 2 of life	Confirmed decrease > 40% at 36½ wk. no induction then because mother did well, induction 2 wk. later for hypertension
4	39	7/6	Chronic hypertension, twins	Spontaneous labor	Twin A, 2,100 grams, Apgar 8/8, survived; Twin B, 2,400 grams, stillborn, macerated	Normal
5	21	2/0	Chronic hypertension, twins	Spontaneous labor	Twin A, 1,410 grams, stillborn; Twin B, 2,850 grams, Apgar 5/8, died on day 3 of life of sepsis	Normal
6	17	1/0	Chronic hypertension, twins	Premature labor	Twin A, 1,315 grams, Apgar 3/7, survived; Twin B, 1,300 grams, Apgar 2/6, version, extraction, neonatal death on day 2 of life of intracranial and pulmonary hemorrhage	Normal
7	30	2/1	Chronic hypertension, massive obesity, previous stillborn	Spontaneous labor	Twin A, 2,830 grams, Apgar 8/9, survived; Twin B, 2,700 grams, stillborn, macerated	Confirmed decrease > 40% at 39 wk. when mother went into spontaneous labor
8	35	5/4	Diabetes mellitus, chronic renal disease, hypertension	Premature rupture of membranes, spontaneous labor	1,930 grams, Apgar 2/6, neonatal death on day 2 of life of hyaline membrane disease	Confirmed decrease > 40% not known until mother was in labor

and newborn infants. At 32 weeks' gestation of the study pregnancy, she was admitted to the High-Risk Obstetric Unit because of hypertension (140/100) and possible fetal growth retardation. With bed rest, her blood pressure became normal. Nine days after admission a sonogram was obtained. The biparietal diameter of the fetal head was 72 mm., corresponding to only 28 weeks' gestation of a normal pregnancy. Amnionic fluid for measurement of the L/S ratio was not obtained, and a decision to effect delivery of this markedly growth-retarded fetus was not made. Five days after sonography, fetal death occurred. Five plasma estrogen levels were available for retrospective analysis. In each plasma sample immunoreactive estrogens were either undetectable or very low (Fig. 3).

Case 9. A 26-year-old white primigravida was admitted at 32 weeks because of generalized edema and hypertension. After 3 days in the High-Risk Obstetric Unit, she became normotensive and was, erroneously, discharged. Three weeks later she was readmitted with recurrent hypertension and a weight gain of 8 pounds during the preceding 2 week period. By sonographic cephalometry, a biparietal diameter of 88 mm. was measured which was considered appropriate for the gestational age. On the day labor began, fetal heart tones had been heard, but at the time of admission to the Labor Unit, they could not be detected. This woman delivered a 2,090 gram, small-for-gestational-age stillborn infant. Retrospectively, it can be recognized (Fig. 3) that a decrease in plasma immunoreactive estrogens had occurred which was greater than 40 per cent and was confirmed. However, if this case had belonged to Group A, the final result would not have been available to the physicians until the day of fetal death.

Case 10. A 17-year-old black primigravida was admitted to the High-Risk Unit at 35 weeks' gestation because of hypertension. At the time of fetal death, 12 days after admission, the biparietal diameter of the fetal head was 81 mm., confirming marked fetal

Table VI. Perinatal deaths, Group B

Case No.	*Age*	*Gravidity parity*	*Indication for monitoring*	*Termination of pregnancy*	*Outcome*	*Estrogen pattern*
1	20	1/0	Fetal growth retardation	Oxytocin induction	650 grams, stillborn, hydrocephalic	Undetectable levels
2	21	4/3	Chronic hypertension, twins	Repeat elective cesarean section	Twin A, 2,115 grams, Apgar 8/9, multiple congenital anomalies (renal agenesis, syringomyelia), neonatal death on day 5 of life; Twin B, 2,480 grams, Apgar 9/9, survived	Confirmed decrease > 40% at 36 weeks
3	15	1/0	Hypertension, twins	Spontaneous labor	Twin A, 1,890 grams, stillborn; Twin B, 2,530 grams, Apgar 6/10, survived	Normal
4	20	2/1	Unsure duration of gestation, twins, obesity	Premature labor	Twin A, 2,220 grams, stillborn, intrapartum death; Twin B, 2,170 grams, Apgar 9/9, survived	Normal
5	22	1/0	Hypertension, obesity	Oxytocin induction	3,175 grams, Apgar 2/1, neonatal death in first hour of life due to resuscitation trauma: bilateral pneumothorax	Low normal, confirmed drop > 40% at 43 weeks
6	16	1/0	Hypertension	Spontaneous labor	1,190 grams, stillborn, macerated; mother had left hospital against medical advice at 30 weeks	Decrease > 40% *not* confirmed
7	39	8/5	Chronic hypertension	Premature rupture of membranes cesarean section	1,430 grams, Apgar 5/6, neonatal death on day 5 of life of hyaline membrane disease and pneumothorax	Decreased
8	38	4/3	Fetal growth retardation hypertension	Spontaneous labor	1,110 grams, stillborn	Very low
9	26	1/0	Hypertension	Spontaneous labor	2,090 grams, stillborn	Low, confirmed decrease > 40% not known until fetal death occurred
10	17	1/0	Hypertension	Oxytocin induction	1,725 grams, stillborn	Confirmed decrease > 40% not known until day of fetal death

growth retardation. The immunoreactive estrogen level had decreased (Fig. 3) but the result of the plasma sample confirming this decrease would not have been known until the day of fetal death even if the case belonged to Group A.

Comment

Following the marked reduction in maternal mortality rates that has occurred during the past 50 years, the chief aim of today's obstetricians and neonatologists has been to effect a similar reduction in perinatal mortality and morbidity rates. Improvement in maternal prenatal care and diagnosis together with advances in neonatal care have been associated with significant reductions in perinatal deaths. Nevertheless, far too many perinatal deaths still occur: in some instances before labor because timely delivery is not accomplished; during labor, when fetal distress is not recognized; and during the neonatal period, more commonly because the fetus is delivered before it has reached maturity. To prevent some of these deaths, the utilization of a number of diagnostic tools have been suggested which promised to provide the obstetrician with greater insight in recognizing impaired fetal well-being.

Measurement of urinary estrogens in pregnant women as a management tool was proposed after it was recognized that the urinary excretion of these hormones decreased shortly before fetal death.[2, 11] It was also established that the incidence of perinatal death was higher in patients with low estrogen values than in those with normal values.[12–15] A number of laboratories found that steroids arising from the fetal adrenal contributed a large proportion of the precursors of placental estrogens that ultimately appear in maternal blood and are later excreted into urine.[16–18] For these reasons, many investigators have hoped that through the use of estrogen and especially estriol measure-

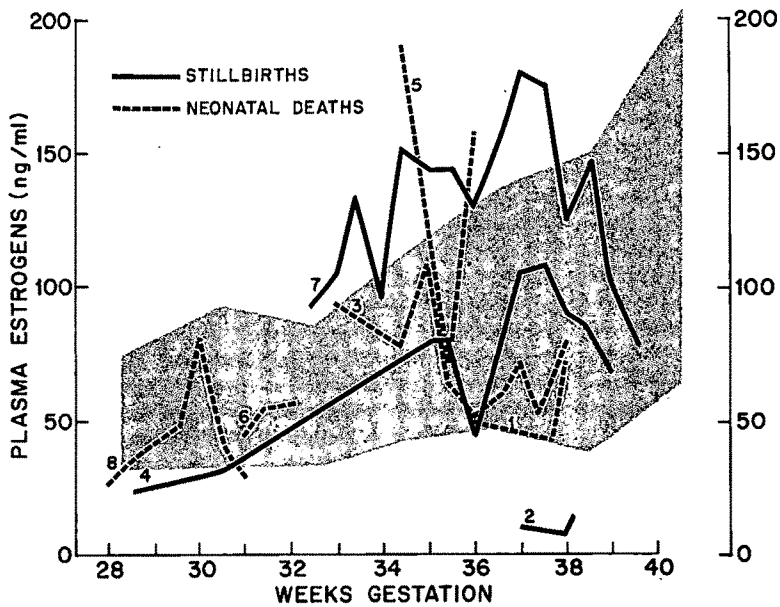


Fig. 2. Perinatal deaths, Group A. Numbers refer to cases in Table V. Shaded area includes ± 1 standard deviation of estrogen levels in normal gravidas.

ments, it would be possible to recognize those fetuses in distress or those who were existing in a compromised environment when simple, clinical data did not allow this diagnosis or conclusion. Thus, on the basis of two hypotheses, the management of patients with a fetus at high risk has been guided by results of estrogen measurements: (1) falling or low estrogen levels indicate fetal distress, and (2) normal estrogen values suggest fetal well-being.

In formulating the design of the present study, we did not question that fetal well-being or distress is commonly associated with low maternal estrogen levels. Rather, the question we asked was whether the measurement of estrogen levels will provide data helpful to the obstetrician in determining the timing of delivery in an individual pregnancy in which the fetus is at high risk. Alternatively, we have considered the possibility that estrogen levels may, in fact, mislead the obstetrician and may contribute to inappropriate intervention in some pregnancies and unfortunate procrastination in others.

In order to evaluate if utilization of plasma estrogen levels would result in a decrease of perinatal deaths, a prospective approach was used which was based on the random assignment of patients to two groups of nearly equal size. In one group, estrogen concentrations were measured and reported to the physician; in the other, the estrogen levels were also measured but not reported.

In the study design, the incidences of fetal and neonatal death serve as objective indicators of failure or success of the diagnostic regimen: if the hypotheses are correct, one would expect more fetal deaths in the control or Not Reported group and among those patients whose estrogens were reported to be abnormal, but in whom physicians refused to effect delivery. If the diagnostic regimen is of no utility in clinical management, no differences would be observed in perinatal deaths between both groups. If, on the other hand, the utilization of plasma estrogens in determining the management of pregnancies with a fetus at high risk is misleading, one could anticipate an excess of neonatal deaths in the Reported Group compared to the Not Reported Group.

The method of Gurpide and associates[5] in which immunoreactive estrogen is measured was selected from the numerous methods available because (1) predominantly estriol is measured, (2) hydrolysis is not required, (3) only one plasma extraction is needed, and (4) a large number of samples can be processed daily by a single technician. In these respects, the method was superior to the existing procedures measuring specifically free or conjugated estriol. Although the method of Gurpide measures nine different estrogens, a close correlation between urinary estriol excretion rates measured by a gas-liquid chromatography and by the immumoreactive method has been established ($y = 1.68 \times -4.36$; $r = 0.950$).[5] The correlation between estrogen excretion and levels in plasma measured with this method in normal patients is also good

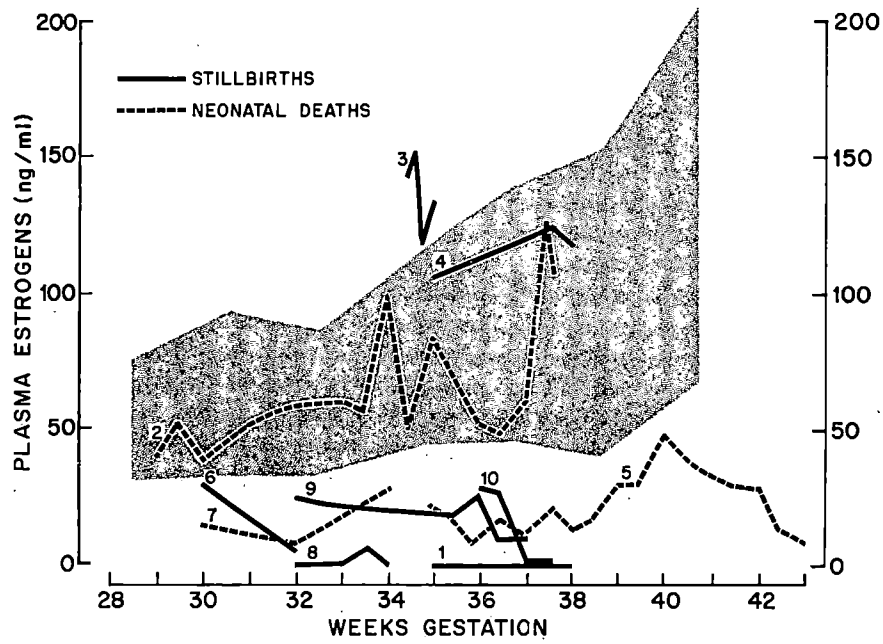


Fig. 3. Perinatal deaths, Group B. Numbers refer to cases in Table VI. Shaded area includes ± 1 standard deviation of estrogen levels in normal gravidas.

(y = 0.33 × +0.99; r = 0.935).[5] Since the interconversion of free and conjugated estrogens and their urinary and plasma profiles in normal and abnormal pregnancies is not well known, a theoretical objection against the method is that the measured levels of immunoreactive estrogens may not be a reflection of fetoplacental estrogen production. However, the same objection can be made against any method that attempts to measure free estriol or one of several conjugates. Indeed, the only way to avoid this dilemma would be to measure the plasma production rate of estriol. As a matter of fact, intuitively, a method which measures multiple estrogens and their metabolites all presumed to have arisen from the placenta and principally from the utilization of fetal precursors is more likely to reflect fetal health since spurious aberrations in maternal estrogen metabolism will be mitigated.

The difficulty in obtaining accurately collected 24 hour urine specimens as well as the difficulty in repeat 24 hour urine sampling were arguments for the selection of plasma rather than urine as a source of estrogen measurement.

The selection of a certain estrogen pattern or level which would dictate to physicians when to effect delivery was obviously critical to the design of the study. Too narrow a definition in such a protocol may lead to a delay of delivery and therefore fetal death; too broad a definition may lead to inappropriately advised early induction of delivery and unnecessary neonatal deaths. After a thorough review of the literature and a consideration of values and patterns in normal patients, a confirmed drop of 40 per cent or more from previous values and repeated measurements under 20 ng. per milliliter after 34 weeks were considered reasonable to advise physicians to effect delivery.

Although the decision to effect delivery in the women of Group A was influenced by the results of estrogen measurement in 16 instances, in an equal number of women in both Groups A and B, delivery was effected electively. This may indicate that in a similar number of Group A cases estrogen values led to elective termination of pregnancy as they may have led to a delay of delivery.

In the present study, knowledge of immunoreactive estrogen levels did not result in an improvement of perinatal mortality rates in the Reported Group over that of the Unreported Group. Among the 19 deaths, there were two cases in which abnormal estrogen patterns might have led to earlier delivery if these had been considered in the total context of the clinical picture. Only one fetal death occurred in which estrogens were the only indicator of impending problems. This may have been avoided if the results of immunoreactive estrogen measurements had been available more frequently than twice weekly. If one assumes that all pregnant women in this study had been followed with daily estrogen measurements

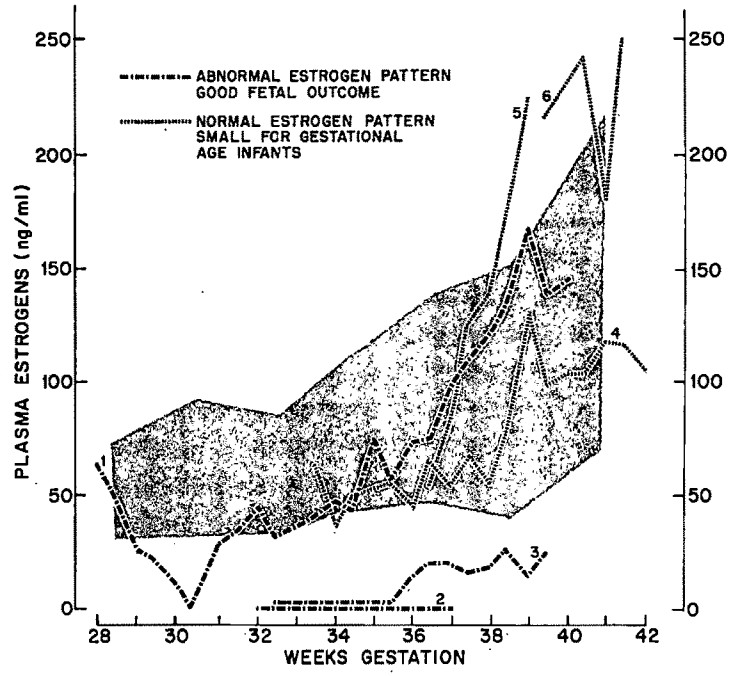


Fig. 4. Examples of women with abnormal estrogen patterns and good fetal outcome who were not taking any medications known to suppress estrogen levels and women with normal estrogen patterns who delivered small-for-gestational-age infants. Shaded area includes ± 1 standard deviation of estrogen levels in normal gravidas.

instead of sampling twice weekly, 18 *additional* samples per patient or 11,200 more assays would have been performed. At a cost of $25.00 per assay, the *additional* expense would have been about $280,000.

From the perinatal deaths in the two groups, five of the nine in Group A and three of the 10 in Group B occurred in women with twin pregnancies, who also had another pregnancy complication. From the data in Tables V and VI and Figs. 2 and 3, it is apparent that none of these deaths could have been prevented through utilization of plasma estrogens.

The true dilemma of the dependency on estrogen levels as a diagnostic tool in the management of women with a fetus at high risk is apparent from the fact that 10 women of the Not Reported Group B would have been delivered 28 days or more prematurely if these pregnancies had been managed solely on the basis of abnormal immunoreactive estrogen levels. In Fig. 4 three representative examples of the 53 women from both groups who had abnormal estrogen levels, but *no* clinical abnormalities suggesting a compromise of fetus or placenta are illustrated. If the decision for early delivery is based exclusively on an abnormal estrogen pattern, perinatal deaths may result for which this diagnostic tool must be incriminated.

In addition to these erroneous diagnoses of fetal distress, there were several instances in which immunoreactive estrogen patterns were entirely normal (Fig. 4; Cases Nos. 4, 5, and 6), although during examination of the newborn infant clear evidence of fetal growth failure was apparent. This demonstrates clearly that some cases of fetal growth failure cannot be recognized from plasma estrogen levels. Thus, if delivery is effected electively singularly on the basis of falling or low plasma estrogen levels, disregarding clinical findings, perinatal deaths are likely to occur as a result of this management. Furthermore, the diagnosis of sufficient fetal distress to cause growth retardation cannot be made in some cases by determining plasma immunoreactive estrogen levels.

This study has been concerned with the evaluation of *plasma* immunoreactive estrogens—mainly estriol—as a diagnostic tool in the evaluation of fetal health. Levitz and associates[19] have shown a large variation in plasma estriol measurements among several samples obtained from the same woman during a 48 hour period. This great variation in plasma estriol levels is not surprising when one considers the fact that a multitude of enzyme systems in fetus, placenta, and mother can influence this level.

One could argue that the preferred test is the measurement of estriol in 24 hour urine specimens, since the total estriol production during a 24 hour period would be reflected by this measurement, thus

avoiding the variations in plasma estrogens that occur during the day, and that may result from positional and activity changes. On the other hand, the good correlation that is found between urinary estriol excretion and plasma levels with a variety of techniques as well as the difficulty of obtaining accurate and complete 24 hour urine collections negates the validity of this argument. The potential danger in patient management for those who rely heavily on urinary estriol determinations—namely, an increase in neonatal deaths due to erroneous early delivery—should be evaluated in a prospective controlled study, designed to ascertain whether with this tool more fetuses are salvaged than lost.

Considering the enormous costs of tests that reputedly monitor uteroplacental function and fetal well-being, it behooves us to consider carefully whether such tests, in fact, contribute to a better understanding of a given patient than we can achieve by time-honored and proved clinical methods.

One such test is the measurement of human placental lactogen (HPL) in plasma of pregnant women. In a recent study, Spellacy and associates[20] reported on the effectiveness of HPL measurements in decreasing fetal deaths. Several questions have to be raised concerning this report, which actually contains two studies: (1) a retrospective analysis of 71 fetal deaths and (2) a prospective analysis of 2,733 pregnancies with a fetus considered to be at high risk. In the retrospective study, 35 instances of fetal deaths (49.3 per cent) occurred although HPL values were not in what the authors considered to be the "fetal danger zone." We analyzed the remaining 36 cases and found that if one excludes those fetuses who suffered malformations and those in which sufficient clinical information was available that would have led us to effect delivery, e.g., diastolic pressures over 110, diastolic pressures over 90 with albuminuria, or severe fetal growth retardation (fetal weight under 1,000 grams at more than 30 weeks' gestation), then only eight fetal deaths remain in which low HPL values were the only indication of a problem given in the report. Thus of 71 fetal deaths, 11.3 per cent, or of the 35 deaths with HPL in the "danger zone," 22.2 per cent may possibly have been salvaged if HPL had been utilized. An analysis of the prospective part of the study is very difficult from the data of the report, since the perinatal mortality rates for the treated and for the control groups are *not* given, but only the fetal and neonatal deaths of those women who had HPL values in the "fetal danger zone." Here, though, the difference is striking: only 2.6 per cent fetal deaths in the treated vs. 14.2 per cent in the control group were found, whereas from the prospective study one would not expect a decrease of the fetal deaths of more than 15 per cent. A detailed description of the 19 cases of the prospective study in which fetal deaths occurred may have allowed the critical reader of the report to arrive at the same conclusions as the authors. From the data presented, however, this is not possible.

The establishment of a correlation between fetal condition and/or outcome and the abnormal results of a fetoplacental function test is insufficient to establish the utility of these tests. The critical question is whether a test provides information not known; and moreover, whether such information can assist in the management of an individual patient, and lastly, whether the use of the test will result in decreased perinatal death and/or morbidity.

The results of the present study are consistent with the view that the knowledge of plasma immunoreactive estrogen levels did not improve perinatal mortality rates in gravidas whose fetus is considered at high risk. Moreover, the results suggest that increased perinatal deaths and morbidity may occur if patient management protocols rely heavily or exclusively upon immunoreactive estrogen levels in determining the timing of intervention in these pregnancies.

Considering simultaneously the zeal of the obstetrician to optimize fetal outcome together with the inordinate cost and unproved utility of all currently used tests that reportedly monitor fetal well-being, it is incumbent upon us to validate all such tests by unbiased, prospective controlled studies in order that we may establish or deny their place in the management of the gravida whose fetus is considered at risk.

The technical assistance of Mr. Shelton Ragland is gratefully acknowledged as well as the cooperation of interns and residents from the Obstetrical Services of Parkland Memorial Hospital.

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Bacterial growth inhibition by amniotic fluid

V. Phosphate-to-zinc ratio as a predictor of bacterial growth–inhibitory activity

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Human amniotic fluid has been shown to contain an inorganic bacterial growth-inhibitory component, zinc. The average zinc concentration in amniotic fluid was 0.44 μg per milliliter. The phosphate concentration of amniotic fluid appears to determine the expression of zinc inhibitory activity. The average phosphate concentration was 92 μg per milliliter. For 22 fluid samples tested, a phosphate-to-zinc ratio of 100 or less predicted a bactericidal fluid. A ratio between 100 and 200 predicted a bacteriostatic fluid. A ratio of greater than 200 predicted a noninhibitory fluid. The possible clinical significance of the ratio is discussed.

PREVIOUS RESEARCH from our laboratory has shown that a wide variety of antibacterial compounds are present in human amniotic fluid.[1–4] Although inhibitory compounds are present, we have shown that fluids of the same or differing gestational ages may vary in their antibacterial activities.[5] Further, several investigators have shown that pathogenic bacteria may be cultured from amniotic fluid in the presence of intact membranes.[6–8] Therefore, it is necessary to identify fluids wich do not inhibit bacterial growth in order to identify the fetus at risk of intrauterine infection.

We have previously shown that the bacterial growth–inhibitory activity of amniotic fluid is reversed by the addition of phosphate[9, 10] and that it is removed by adsorption to bentonite or negatively charged bacterial cells.[10] We have also shown that the component is resistant to boiling for 30 minutes.[10] Such properties may be associated with cationic peptides[11–14] or inorganic cations.

The purpose of this investigation was to demonstrate that an inorganic inhibitor is present in amniotic fluid and to develop a procedure to identify the fetus at risk of intrauterine bacterial infection.

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Material and methods

Amniotic fluid. Amniotic fluid samples of varying gestational durations were obtained aseptically by transabdominal amniocentesis from obstetric patients at the University of Iowa Hospitals. Samples containing blood or those from patients receiving antibiotics were excluded. Prior to use, each fluid was sterilized by Millipore filtration* (pore size, 0.45 μM) and tested for antibacterial activity.[5]

Organism. *Escherichia coli,* type 06, was the test organism used throughout this study. Starter cultures were grown in trypticase soy broth† for eight hours and then diluted to give an inoculum size of between 10^3 and 10^4 cells per milliliter. Bacterial growth-inhibitory activity was measured with the previously described plate-count technique.[5] Controls consisted of bacterial growth obtained in trypticase soy broth and distilled water.

Standard phosphate solution. The standard phosphate solution used was that in the chemically defined medium described by Larsen and associates.[9]

*Millipore Corp., Ashby Rd., Bedford, Massachusetts 01730.

†Baltimore Biological Laboratory, Cockeysville, Maryland 21030.

Table I. Effect of ultrafiltration on amniotic fluid bacterial growth–inhibitory activity

Weeks of gestation	*Amniotic fluid fraction*	*Inhibitory activity*
19	Unfiltered	0
	Ultrafiltrate	0
	Retentate	0
40	Unfiltered	+
	Ultrafiltrate	+
	Retentate	0
42	Unfiltered	0
	Ultrafiltrate	+
	Retentate	0

Ultrafiltration. Molecular weight estimation and preliminary purification of the antibacterial component of amniotic fluid was accomplished by pressure dialysis with a Diaflo cell equipped with a UM10 membrane* which excludes compounds of greater than 10,000 daltons. To assay for the presence of inhibitory activity in the retentate fluid and filtrate from pressure dialysis, the following procedure was followed. Ten milliliters of fluid was passed through the Diaflo apparatus until 4 ml. remained in the retentate. Both the retentate fluid and filtrate were sterilized by Millipore filtration. Bacterial growth–inhibitory activity and demonstration of adequate nutrition were done according to previously described methods.[5, 15] To show the phosphate-sensitive nature of the bacterial inhibitor, 10 μl of the standard phosphate solution was added to an aliquot of the retentate fluid and filtrate. Both were then assayed for bacterial inhibition.

Proteolytic enzyme treatment. Pronase† and trypsin‡ were added to amniotic fluid UM10 Diaflo filtrates at a concentration of 100 μg of enzyme per milligram of fluid protein. The reaction mixtures were incubated at 37° C. for one hour. Because pronase was found to be toxic to *E. coli,* the digestion mixture plus the pronase control were placed in a boiling water bath for 30 minutes to inactivate the enzyme.

Biochemical assay. Protein was measured by the method of Lowry and colleagues.[16]

Ashing procedure. Amniotic fluid and the UM10 Diaflo filtrates of amniotic fluids were ashed according to the method of Flaschka and co-workers.[17] Samples were dry ashed for 10 hours at 70° C.

*Amicon Corp., Scientific Systems Div., 21 Hartwell Ave., Lexington, Massachusetts 02173.

†Calbiochem, 3625 Medford St., Los Angeles, California 90063.

‡Sigma Chemical Co., 3500 De Kalb St., St. Louis, Missouri 63118.

Noninhibitory control medium. A 10 per cent concentration of a UM10 Diaflo filtrate of amniotic fluid obtained at 19 weeks' gestation served as the noninhibitory control medium (noninhibitory control filtrate).

Quantitative analysis. Zinc concentrations in amniotic fluid were quantitated before ashing with an atomic absorption spectrophotometer.* Zinc standards consisted of dilutions of zinc chloride and contained 0.5, 1.0, 2.0, and 3.0 μg per milliliter of zinc.

Phosphate determination. Phosphate concentrations were measured with a modification of the method Youngburg and Youngburg.[18] One milliliter of amniotic fluid to be tested was mixed with 4 ml. of trichloroacetic acid. Following incubation at room temperature for 10 minutes, the precipitate was pelleted by centrifugation (2,000 × g for 15 minutes). One milliliter of the sulfuric acid–sodium molydate solution was added. The solution was then mixed, and 0.5 ml. of the stannous chloride solution was added. Phosphate concentrations were determined by measuring absorbance at 660 nm. after two minutes. Standard solutions consisted of potassium phosphate in deionized distilled water with phosphate concentrations ranging from 0 to 200 μg per milliliter.

Results

The effects of ultrafiltration of amniotic fluid samples of 19, 40, and 42 weeks' gestation are summarized in Table I. Amniotic fluid samples from pregnancies of 19 weeks or less failed to show bacterial growth–inhibitory activity in the unfiltered amniotic fluid, UM10 Diaflo filtrates, or UM10 Diaflo retentate material. A 10 per cent concentration of the UM10 Diaflo filtrate from this fluid showed good growth and was used as the noninhibitory control medium (see "Material and methods" section).

The UM10 filtrates of amniotic fluid from pregnancies of approximately 40 weeks were consistently bactericidal while unfiltered fluid varied from bacteriostatic to bactericidal, indicating that a bacterial growth–inhibitory component of molecular weight less than 10,000 was present. The bactericidal activity seen was effectively reversed either by addition of phosphate or by dilution with sterile deionized distilled water according to the method of Larsen and associates.[15]

Unfiltered amniotic fluid samples from gestations of 42 weeks or more varied in bacterial growth inhibition. The activities varied from noninhibitory to occasionally

*Perkin-Elmer Corp., Instrument Div., 800 Main Ave., Norwalk, Connecticut 06852.

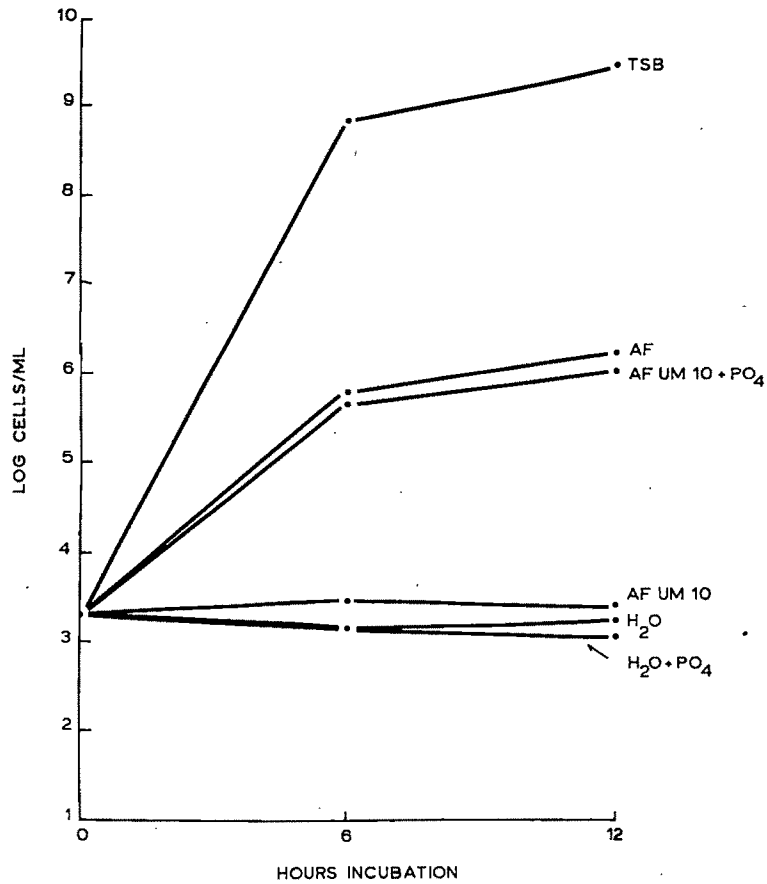


Fig. 1. Demonstration of the ability of phosphate to block the bacterial growth–inhibitory activity of amniotic fluid of 42 weeks' gestation. The unfiltered fluid *(AF)* supports bacterial growth. Upon ultrafiltration, the UM10 Diaflo filtrate *(AF UM 10)* is bacteriostatic but contains 17 μg less phosphate per milliliter than the unfiltered fluid. The addition of 17 μg of phosphate back to a milliliter of UM 10 Diaflo filtrate *(AF UM 10 + PO_4)* reverses the bacterial inhibition observed. Trypticase soy broth *(TSB)*, disilled water *(H_2O)*, and distilled water plus phosphate *($H_2O + PO_4$)* served as controls.

bactericidal. The UM10 Diaflo filtrates of these same fluids were always bacteriostatic or bactericidal, and the inhibitory activity was sensitive to the addition of phosphate and dilution with sterile deionized distilled water.

The increased bacterial growth–inhibitory activity observed in the UM10 Diaflo filtrate from amniotic fluid at 42 weeks' gestation may be due to lowering of the phosphate concentration by filtration. Fig. 1 shows that unfiltered amniotic fluid from a gestation of 42 weeks, which conatained 67 μg of phosphate per milliliter, was noninhibitory to bacterial growth, while the UM10 Diaflo filtrate, which contained 50 μg of phosphate per milliliter, was bacteriostatic. When the 17 μg of phosphate per milliliter was again added to the UM10 Diaflo filtrate, the filtrate supported bacterial growth similar to that in the unfiltered fluid. We tested other fluids and obtained similar results.

To determine if the phosphate-sensitive inhibitor contained in the ultrafiltrate of amniotic fluid was a cationic peptide, we attempted to destroy the inhibitory activity by incubation with pronase and trypsin. Fig. 2 demonstrates that the bacterial inhibitor was resistant to pronase digestion. Boiling was observed to enhance antibacterial activity, confirming our previously reported data.[10] The addition of phosphate following pronase digestion and boiling again allowed bacterial growth. Similar results were obtained with trypsin digestion. These data suggest that the bacterial inhibitor may not be a peptide but an inorganic compound.

Therefore, an inhibitory UM10 Diaflo filtrate was dry ashed, reconstituted in the noninhibitory control medium, and then assayed for bacterial growth–inhibitory activity. Fig. 3 demonstrates that the ashed material from the inhibitory filtrate contained an

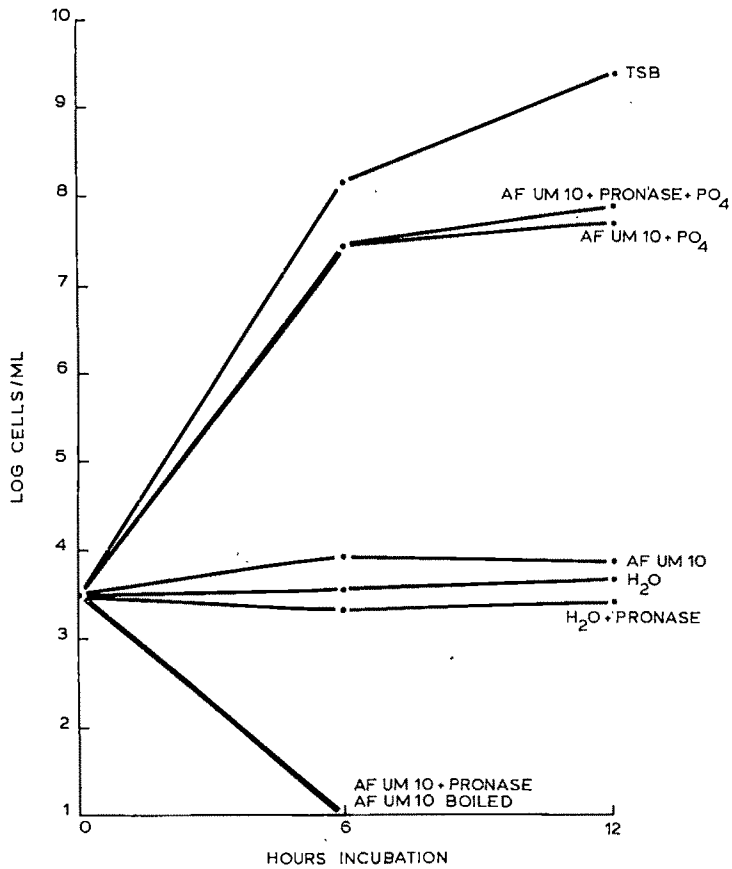


Fig. 2. The effect of pronase on the antibacterial activity of a UM10 Diaflo filtrate is shown. The UM 10 Diaflo filtrate *(AF UM 10)* is bacteriostatic. When the UM10 Diaflo filtrate was boiled *(AF UM 10 BOILED)* or treated with pronase and then boiled *(AF UM 10 + PRONASE)*, the filtrate becomes bactericidal. The inhibition after pronase digestion is reversed by phosphate *(AF UM 10 + PRONASE + PO_4)*. Trypticase soy broth *(TSB)*, distilled water *(H_2O)*, and distilled water + pronase *(H_2O + PRONASE)* served as controls.

antibacterial component, which was also sensitive to the addition of phosphate.

It has been shown that certain trace metal cations in a low concentration inhibit bacterial growth.[19, 20] Of the potentially inhibitory trace metals, only zinc has been previously reported in amniotic fluid.[21] This was verified in our laboratory with standard qualitative analytical techniques.[22, 23]

The concentration of zinc in 22 fluid samples was then quantitated with atomic absorption spectrophotometry. The concentrations of zinc in the fluid samples tested ranged from 0.17 to 2.15 μg per milliliter, with an average concentration of 0.44 μg per milliliter (Table II). To test whether the zinc contained in amniotic fluid was sufficient to account for inhibitory activity, we added varying concentrations of zinc to the noninhibitory control filtrate and assayed for inhibitory activity. Fig. 4 shows that when 0.08 μg or more of zinc per milliliter were added to the noninhibitory control filtrate increasing antibacterial activity occurred. All fluid samples examined to date have greater than 0.08 μg of zinc per milliliter and, therefore, should be inhibitory if the concentration of zinc alone determines inhibitory activity.

However, we have previously shown that amniotic fluid of the same or different gestational ages varies in its capacity to inhibit bacterial growth.[5] Also, we have shown that phosphate added to fluids[9, 10] or phosphate contained in fluids alters the bacterial growth–inhibitory activity. Because of this, we believe that phosphate present in amniotic fluid may interact with zinc and be responsible for the variable inhibitory activity. The phosphate concentration in the same 22 amniotic fluid specimens was determined and was found to range from 14 to 200 μg per millimeter, with a mean phosphate concentration of 92 μg per milliliter. A ratio of the concentration in milligrams of phosphate to the concentration in milligrams of zinc was estab-

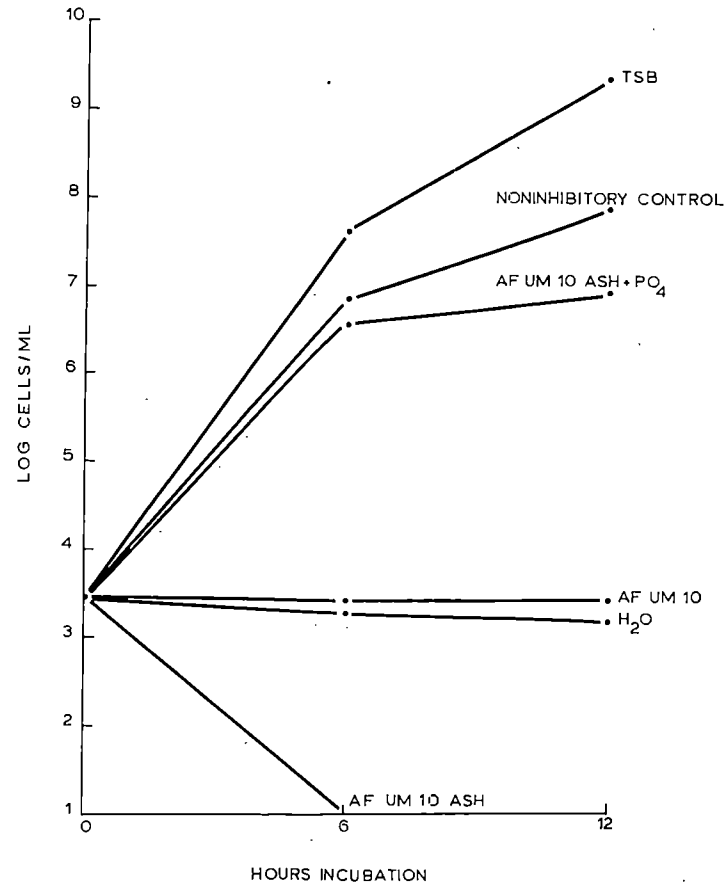


Fig. 3. The effect of ashing a UM 10 Diaflo filtrate on antibacterial activity. The UM 10 Diaflo filtrate *(AF UM 10)* was bacteriostatic before ashing. The reconstitution of ashed UM 10 Diaflo filtrate in a noninhibitory control filtrate *(AF UM 10 ASH)* results in bactericidal activity. The bactericidal activity is reversed by the addition of phosphate *(AF UM 10 ASH + PO_4)*. The noninhibitory control filtrate *(NONINHIBITORY CONTROL)*, trypticase soy broth *(TSB)*, and distilled water *(H_2O)* served as controls.

lished as a predictor of amniotic fluid–inhibitory activity.

Table II shows the concentrations of zinc and phosphate as well as the correlation of the phosphate-to-zinc ratio with inhibitory activity. Fluids with a phosphate-to-zinc ratio of 100 or less were bactericidal. Fluids with a phosphate-to-zinc ratio of 100 to 200 were bacteriostatic, and fluids with a phosphate-to-zinc ratio of greater than 200 were noninhibitory. Table III summarizes these data.

Comment

Many antibacterial compounds have been identified in amniotic fluid. Among these are lysozyme, peroxidase, transferrin, and immunoglobulin.[1–4] All are proteins and have molecular weights greater than 10,000 daltons. In this investigation we demonstrated that an inorganic ion, zinc, is inhibitory to bacterial growth in amniotic fluid. Because the larger–molecular weight proteins are not present in the ultrafiltrate and the retentate material from inhibitory fluids is consistently less inhibitory, lysozyme, peroxidase, transferrin, and immunoglobulin may play only a minor role in the capacity of amniotic fluid to inhibit bacterial growth.

Metal cations, including zinc, when present in very low concentrations inhibit the growth of *E. coli* in a chemically defined medium.[20] These metals probably interfere competitively with bacterial metabolic processes which require magnesium, presumably because of similar ionic radii and charges. We confirmed the presence of zinc in amniotic fluid and determined the zinc concentrations in 22 amniotic fluid samples; we found an average of 0.44 μg per milliliter, with all fluids containing 0.17 μg per milliliter or greater. We also found that 0.08 μg of zinc per milliliter was the minimum inhibitory concentration of zinc in the noninhibitory control filtrate but that zinc alone does not ensure that amniotic fluids will be inhibitory.

Table II. Correlation of phosphate-to-zinc ratio with antibacterial activity

Fluid No.	*Zinc (μg/ml.)*	*Phosphate (μg/ml.)*	*Phosphate/zinc*	*Inhibitory activity*
1	2.15	48	22	Bactericidal
2	0.25	14	56	Bactericidal
3	0.33	26	80	Bactericidal
4	0.21	20	100	Bactericidal
5	0.41	110	75	Bactericidal/ bacteriostatic
6	0.18	24	133	Bacteriostatic
7	1.17	180	154	Bacteriostatic
8	0.71	110	155	Bacteriostatic
9	0.34	53	156	Bacteriostatic
10	0.41	66	162	Bacteriostatic
11	0.49	84	172	Bacteriostatic
12	0.17	32	188	Bacteriostatic/ noninhibitory
13	0.32	80	250	Noninhibitory
14	0.39	102	262	Noninhibitory
15	0.20	54	270	Noninhibitory
16	0.44	141	320	Noninhibitory
17	0.32	107	333	Noninhibitory
18	0.34	155	457	Noninhibitory
19	0.24	133	554	Noninhibitory
20	0.35	200	571	Noninhibitory
21	0.17	110	647	Noninhibitory
22	0.22	185	841	Noninhibitory
Average	0.44	92		

Table III. Correlation of phosphate-to-zinc ratio with bacterial growth–inhibitory activity

Phosphate/Zinc	*Inhibitory activity*
<100	Bactericidal
100-200	Bacteriostatic
>200	Noninhibitory

Phosphate concentrations in amniotic fluid samples were then determined and found to vary considerably. The average phosphate concentration was found to be 92 μg per milliliter, which is greater than the phosphate concentration reported by Cantarow and colleagues.[24] However, they studied only third-trimester fluid samples, while we studied samples from pregnancies of 16 to 44 weeks' gestation. We found that amniotic fluid samples from gestations of 16 to 20 weeks which are noninhibitory contained high phosphate concentrations and may explain the difference in the average described previously. Although the mechanism of phosphate interference with zinc inhibitory activity is unknown, the ratio seems important. With an increased phosphate concentration, a zinc phosphate precipitate may form and remove the inhibitory component from amniotic fluid.

The interference of zinc inhibitory activity in amniotic fluid by phosphate may also explain the data showing dissimilar inhibitory activity seen in fluid samples of different gestational durations. Amniotic fluid samples from gestations of 19 weeks have very high concentrations of phosphate. Upon ultrafiltration, phosphate is adsorbed by the Diaflo membrane but not in a sufficient quantity for the fluid to be inhibitory.

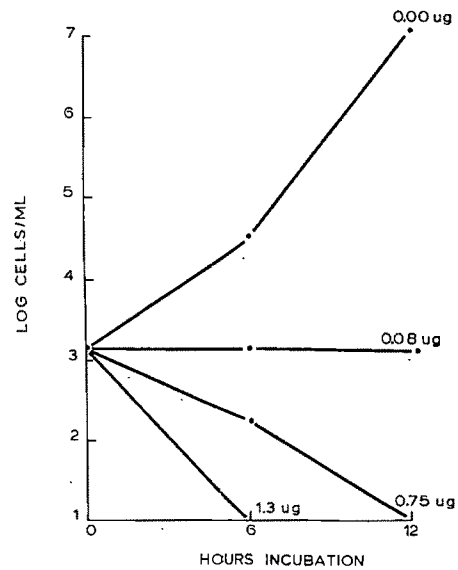


Fig. 4. Determination of the minimum inhibitory concentration of zinc in the noninhibitory control filtrate. The level of zinc required for inhibitory activity in the noninhibitory control filtrate is 0.08 μg per milliliter. Increasing the zinc concentration further increases inhibitory activity.

However, ultrafiltration of the amniotic fluid samples from gestations of 40 weeks does remove sufficient phosphate to increase the inhibitory activity. An unfiltered amniotic fluid sample from a gestation of 42 weeks was noninhibitory with the criteria we previously established.[5] After ultrafiltration, 25 per cent of the phosphate was lost. This phosphate loss reduced the phosphate-to-zinc ratio, and the ultrafiltrate became bacteriostatic.

In this study of 22 amniotic fluid samples, the phosphate-to-zinc ratio was shown to be accurate in predicting the amniotic fluid bacterial growth–inhibitory capacity. Should the ratio continue to be an accurate predictor, it may provide the physician with a useful tool to determine the fetus at risk of intrauterine bacterial infection. More significant may be the importance of dietary supplementation of zinc or the effect of the addition of zinc directly into amniotic fluid to prevent sepsis. These and further studies regarding the antibacterial system present in amniotic fluid are being carried out in our laboratory.

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Bacterial growth inhibition by amniotic fluid

VI. Evidence for a zinc-peptide antibacterial system

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The zinc bacterial inhibitory activity of amniotic fluid is dependent on the presence of a second, organic component contained in amniotic fluid. The second component is heat stable, resists proteolytic digestion, and is present in amniotic fluid throughout pregnancy. Further, the component may be a peptide with a molecular weight of less than 5,000 daltons. Phosphate reversal of amniotic fluid inhibitory activity may result from interference with the organic component rather than zinc.

IN THE PRECEDING paper we demonstrated that zinc is an antibacterial component of human amniotic fluid (AF) and its UM10 Diaflo filtrate.[1] The concentration of zinc necessary for inhibitory activity in an AF noninhibitory control filtrate was found to be 0.08 μg per milliliter. However, Abelson and Aldous[2] found that the concentration of zinc necessary for inhibitory activity in a chemically defined medium (CDM) was 2 μg per milliliter, which is signficantly higher than that in AF.

The discrepancy in the amount of zinc required to inhibit the growth of *Escherichia coli* in the CDM and AF may be due to several reasons. Zinc alone in AF may inhibit bacterial growth by a mechanism different from interference with normal magnesium metabolism which has been reported. Alternatively, the lower concentration of zinc may require a second component contained in AF to inhibit bacterial growth.

The purpose of this investigation was to determine whether zinc alone inhibits bacterial growth or whether a second component is required for inhibitory activity.

Material and methods

Amniotic fluid. Amniotic fluid samples were prepared prior to use as described in the preceding publication.[1] Fluids were concentrated and stored in a lyophilized condition.

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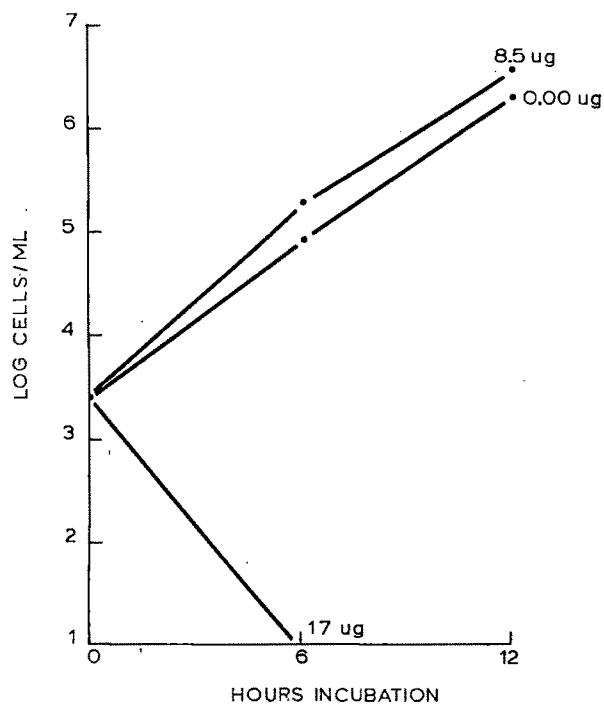


Fig. 1. The minimal inhibitory concentration (MIC) of zinc in a chemically defined medium (CDM). The CDM without added zinc (0.00 μg) supported bacterial growth. Between 8.5 and 17 μg of zinc per milliliter were required for bacterial growth inhibitory activity in the CDM.

Organism. *E. coli* type 06 was the test organism used throughout this study. Viable plate count assays were

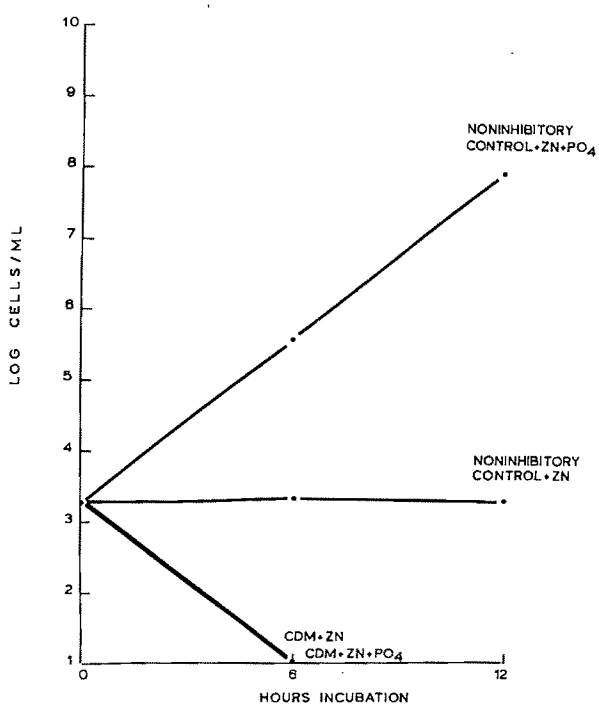


Fig. 2. The effect of phosphate on zinc inhibitory activity in the AF noninhibitory control filtrate and a chemically defined medium (CDM). The noninhibitory control filtrate containing 0.08 μg of zinc per milliliter (noninhibitory control + Zn) was bacteriostatic. The bacteriostasis was reversed by the addition of 10 μl of the standard phosphate solution (noninhibitory control + Zn + PO_4). The CDM containing 17 μg of zinc per milliliter (CDM + Zn) was bactericidal. The bactericidal activity was not reversed by the addition of phosphate (CDM + Zn + PO_4).

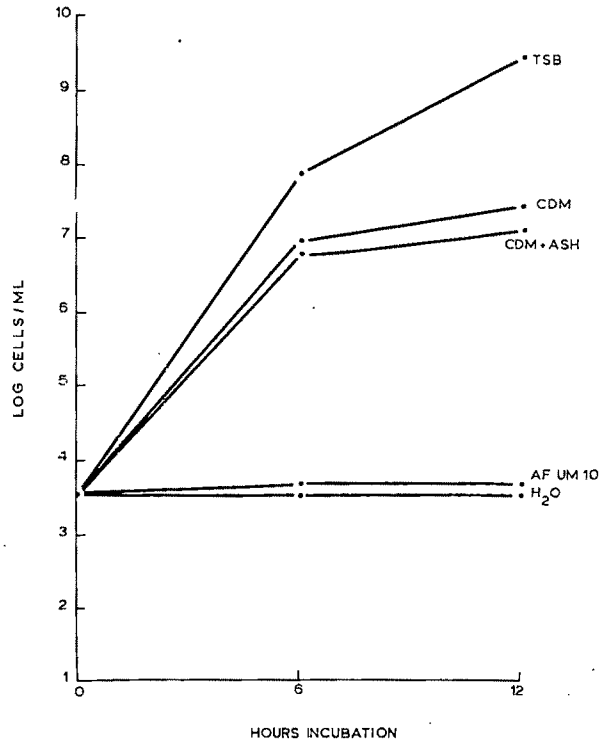


Fig. 3. The effect on bacterial inhibition of the addition of ashed UM10 Diaflo filtrate to the chemically defined medium (CDM). No inhibitory activity is observed when ashed UM10 Diaflo filtrate is added to the CDM (CDM + ASH). The CDM and distilled water (H_2O) served as controls.

performed according to a previously described method.[3]

Ashing procedure. Ashing of UM10 Diaflo filtrate was performed as described by Flaschka and associates.[4]

Noninhibitory control media. The AF noninhibitory control filtrate was prepared as described in the preceding paper.[1] A CDM was prepared with the following composition: 1×10^{-4}M phosphate (potassium phosphate); 4×10^{-4}M magnesium; 1×10^{-4}M glucose; 4×10^{-5}M sodium chloride; and 2×10^{-5}M ammonium sulfate. This medium contained similar phosphate, magnesium, and glucose concentrations as the noninhibitory control filtrate of AF. Zinc was not detectable in either medium. Lysozyme activity was not present in the AF noninhibitory control filtrate.

Biochemical assay. Lysozyme activity was measured by a previously described method.[5] Lysozyme, salt free, 3× crystallized was purchased from Worthington Biochemicals (Freehold, New Jersey). *Micrococcus lysodeikticus* was purchased from Sigma Chemical Co. (St. Louis, Missouri).

Column chromatography. A 15 ml. sample of an inhibitory UM10 Diaflo filtrate was lyophilized and then reconstituted to 3.5 ml. with deionized distilled water. Particulate material was removed by centrifugation (2,000 × g, 15 minutes). The supernatant fluid was chromatographed on a Sephadex G-25, Pharmacia Fine Chemicals (Piscataway, New Jersey), column (2.5 by 40 cm.) and eluted with deionized distilled water. Effluent material was collected in 3 ml. fractions and was monitored for absorbance at 280 nm. The peak obtained from the column was assayed for bacterial growth inhibitory activity in the AF noninhibitory control filtrate using the viable plate count technique.[3]

Acetone precipitation. Equal volumes of an inhibitory UM10 Diaflo filtrate, Amicon Corp. (Lexington, Massachusetts), and ice cold acetone were mixed. The mixture was incubated for 30 minutes in an ice water bath. The resulting precipitate was sedimented by centrifugation (2,000 × g, 15 minutes). The supernatant fluid was lyophilized. The lyophilized preparation was restored to the original UM10 Diaflo filtrate

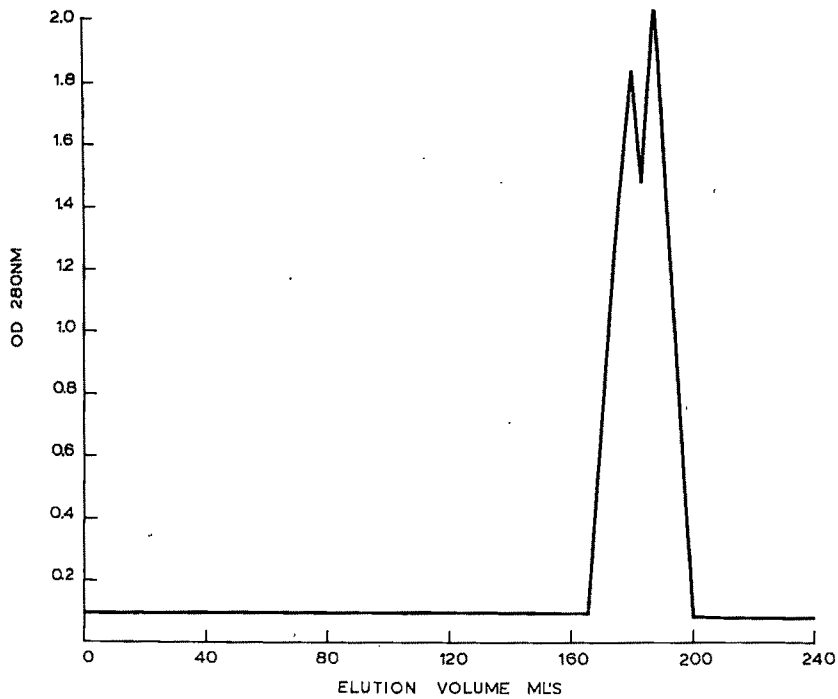


Fig. 4. The elution pattern of Sephadex G-25 column chromatography of an AF UM10 Diaflo filtrate is shown. Fifteen milliliters of UM10 Diaflo filtrate was concentrated to a 3.5 ml. and applied to the column. The effluent was monitored for absorbance at 280 nm. Two overlapping peaks were obtained at almost twice the void volume (Vo = 100 ml.).

Table I. Lysozyme activity in unfiltered AF and the UM10 Diaflo filtrate

AF fraction	*Lysozyme (μg/ml.)*	*Inhibitory activity*
Unfiltered AF	4.9	Bacteriostatic
UM10 Diaflo filtrate	—*	Bactericidal

*No detectable lysis of *Micrococcus lysodeikticus*.

volume and sterilized by Millipore filtration (0.45 μ pore size filter, Millipore Filter Corp. (Bedford, Massachusetts). Bacterial growth inhibitory activity of the preparation was measured by the viable plate count technique.[3]

Results

Abelson and Aldous[2] reported that 2 μg of zinc per milliliter were required for bacterial inhibitory activity in a CDM. Because the AF noninhibitory control filtrate was found to require 25 times less zinc per milliliter for inhibitory activity, we decided to determine the minimum inhibitory concentration (MIC) of zinc in a CDM. Fig. 1 shows that between 8.5 and 17 μg of zinc per milliliter were required for inhibitory activity in the CDM. This concentration of zinc is more than 100 times greater than that necessary for similar inhibitory activity in the AF noninhibitory control filtrate reported previously from our laboratory.[1] While the addition of phosphate to the AF noninhibitory control filtrate containing 0.08 μg of zinc per milliliter effectively reversed the inhibitory activity, the phosphate solution did not reverse the zinc inhibition when added to the CDM containing 17 μg of zinc per milliliter as seen in Fig. 2.

Because of differential zinc concentrations for inhibition of bacterial growth between CDM and the AF noninhibitory control filtrate and the failure of phosphate to reverse the inhibition in the CDM, there may be a second component in AF associated with zinc to inhibit bacterial growth. Therefore, studies were undertaken to verify the presence and determine the biochemical nature of the second component.

To ascertain whether the second component was organic or inorganic, we ashed an inhibitory UM10 Diaflo filtrate of AF and reconstituted the ash to its original fluid volume with CDM and assayed for bacterial inhibition. The data shown in Fig. 3 suggest that the second component is an organic compound because the ash does not inhibit *E. coli* in the CDM as was observed when the ash was added to a noninhibitory control filtrate of AF.[1]

Lysozyme as the second component was investigated

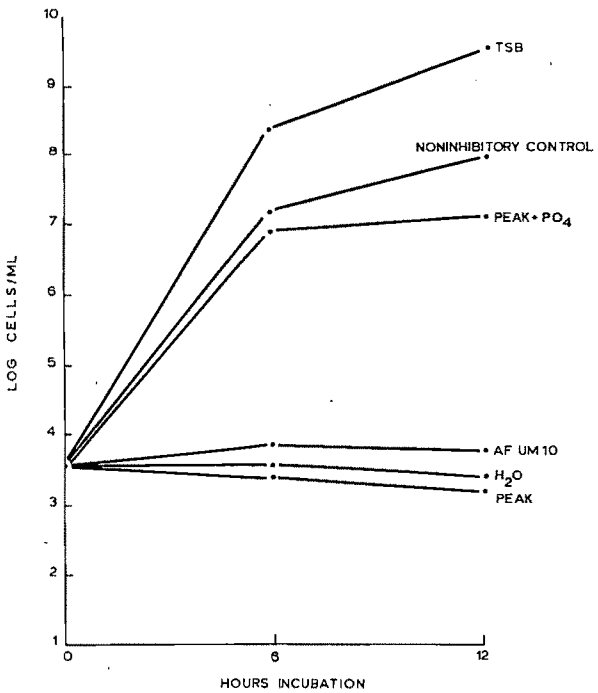


Fig. 5. Bacterial growth inhibitory activity of the concentrated elution peak from G-25 Sephadex chromatography is shown. Peak material when added to the noninhibitory control filtrate (Peak) was bacteriostatic and the inhibition was reversed by phosphate (Peak + PO_4). Trypticase soy broth (TSB), unchromatographed UM10 Diaflo filtrate (AF UM10), noninhibitory control filtrate (noninhibitory control), and distilled water (H_2O) served as controls.

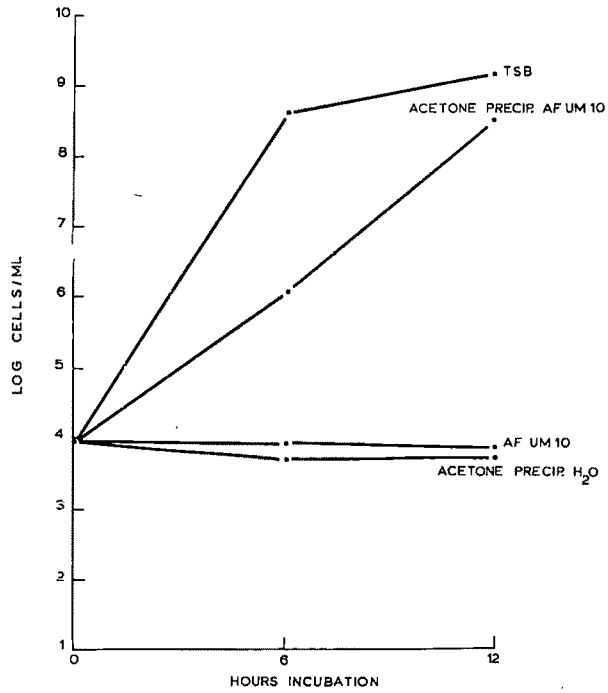


Fig. 6. The effect of peptide precipitation on AF UM10 Diaflo filtrate inhibitory activity (AF UM10). The precipitation of UM10 Diaflo filtrate peptides with 50 per cent acetone reverses the inhibitory activity (Acetone Precipitate AF UM10). Trypticase soy broth (TSB) and acetone precipitated distilled water (Acetone Precip. H_2O) served as controls.

because of its heat stability and resistance to proteolytic digestion and because its molecular weight is near the molecular exclusion limit of the AF UM10 Diaflo filtrate. Table I shows that lysozyme is not the second component, since the UM10 Diaflo filtrate of AF contained no detectable lysozyme activity and was more inhibitory than the unfiltered fluid.

However, the second inhibitor may be a peptide other than lysozyme. Therefore, preliminary isolation of the second component was carried out on a Sephadex G-25 column. Fig. 4 shows the elution pattern obtained. Two overlapping peptide peaks were obtained at approximately twice the void volume (Vo = 100 ml.). Three fractions of the major peak were combined, concentrated, then sterilized by Millipore filtration, and assayed for bacterial inhibitory activity. Fig. 5 demonstrates that the concentrated fraction contained inhibitory activity which was sensitive to phosphate. Analysis of the peak showed that it also contained zinc.

The association of a peptide with zinc in bacterial inhibition was verified by cold acetone precipitation, which removes low molecular weight peptides from solution. Fig. 6 shows that acetone precipitation removed the inhibitory activity of the AF UM10 Diaflo filtrate.

Comment

The zinc-associated bacterial inhibitory activity of AF reported previously appears to be related to the phosphate concentration, but dependent on the presence of a second, organic component. In previous reports we found that AF inhibitory activity resisted heat inactivation[6] and proteolytic digestion.[1] These properties must also be associated with the organic component, as well as zinc, since both are present in AF. Further, the organic component is active even at a 10 per cent concentration of AF since addition of zinc alone to a noninhibitory control filtrate of AF resulted in bacterial inhibition. Phosphate reversal of inhibitory activity appears to be directed at interference with the organic component rather than zinc as initially thought, because zinc inhibition in CDM is not reversed by the addition of phosphate as it is in the noninhibitory control filtrate of AF.

We have provided preliminary data which suggests

that the organic inhibitory component is a low molecular weight peptide. The absorbance peak at 280 nm. from the G-25 column and the acetone precipitation of the inhibitor both suggest peptide involvement.[7] The ultrafiltration studies reported previously showed that the component has a molecular weight of less than 10,000 daltons, but the gel filtration data suggests the component has a molecular weight near 5,000 daltons.

Although the second component is not lysozyme, there are similarities between the physical properties of lysozyme and the second component in AF. Both are heat stable, resistant to proteolytic digestion, and bind a metal. Manganese confers heat stability and resistance to proteolysis upon lysozyme.[8] A similar function may be performed by zinc for the second component in AF.

While the elution peak obtained from gel filtration contained only 0.22 μg of zinc per milliliter, it was inhibitory when added to either distilled water or to the noninhibitory control AF. The peak provided not only zinc to the noninhibitory control AF lowering the phosphate to zinc ratio, but also the organic component, which when associated with zinc has been shown to have antibacterial activity alone. This suggests that the organic component–zinc compound is a naturally occurring antibacterial system. The organic component may be present in AF throughout pregnancy but requires sufficient zinc to become an effective inhibitor.

With this and future research, an understanding of both the inhibitory nature of AF and the unpredictable occurrence of intrauterine sepsis will be gained. The importance of phosphate in affecting the activity of this system is of interest basically, but clinically one should question the indiscriminate use of compounds containing phosphate in pregnancy until more knowledge has been obtained regarding their effects on intrauterine concentration and the antibacterial activity of AF.

In summary, we have shown that zinc may act synergistically with a phosphate sensitive organic component to inhibit the growth of *E. coli.* Although, an organic component appears to be associated with zinc, the phosphate to zinc ratio has continued to be an accurate predictor of antibacterial activity in AF. The organic component is heat stable, resists proteolytic enzyme digestion, and may be a peptide having a molecular weight of approximately 5,000 daltons. Further studies regarding the isolation, purification, and identification of this component are presently being done in our laboratory.

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Classical and "true" gestational postmaturity

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In a study of a sample of 317 conceptional basal body temperature (BBT) curves obtained from normal women, the authors have applied new definitions of prematurity and postmaturity which take into account the time of ovulation. They were thus able to estimate (1) the error rates associated with the classical definitions–incorrect classification as pre- or postmature and nondetection; in particular, for this series, the percentage of incorrectly classified postmatures is high (70 per cent) and is even more so when considering only the unwanted births (80 per cent); (2) the order of magnitude in terms of days of the error made in assessing postmaturity by the classical method. This was found to be quite substantial for the misclassified cases.

IN ORDER to predict the delivery date for his pregnant patients, the obstetrician usually has at his disposal only the date of the last menstrual period (LMP). In addition, the WHO norms defining prematurity and postmaturity as well as the results published in the literature are all based on this date. However, gestation begins with fertilization, and hence series of pregnancies for which the dates of conception, or at least of ovulation, are relatively well known are necessary in order to determine the order of magnitude of the errors usually made in assessing gestational maturity. Such series are rare. The present study was carried out on 317 cases for which the conceptional BBT curve was available.

Material and methods

The conceptional BBT curves from 517 women using the rhythm method were obtained from a family planning center (CLER). The conceptions were either wanted, when the method proved successful, or unwanted, in the case of failure. The last day of the hypothermic phase as defined by Vincent[1] was chosen to represent the day of ovulation and will be referred to as "O" day. Curves during which hormonal treatment was administered were removed from the initial sample as well as those immediately following an abortion or a birth and those corresponding to a miscarriage, a stillbirth, or a multiple pregnancy (in all 91 cases). Curves for which no "O" day could be determined were declared to be illegible (109 curves); in the majority of these cases midcycle temperature readings were missing. Finally, 317 cases were retained for the study.

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Results

For reference, Figs. 1*A*, 1*B*, and 1*C* show the distribution of the interval (OI) between the first day of the LMP and "O" day, for all 317 cases and separately for the wanted and the unwanted births, when this additional information was available—239 and 56 cases, respectively. It is clear that though the mean values of OI for the two types of births are of the same order, the variance for the unwanted births is much greater (50.7 vs. 25.7, $p < 0.01$). This difference can easily be explained by the fact that rhythm failures are often due to an earlier or—more frequently—to a later ovulation than is usual for the woman concerned.

Fig. 2 shows the scatter diagram obtained for all 317 cases when the gestational age counted from the first day of the LMP, here referred to as menstrual age (MA), is plotted against OI. The horizontal lines represent the classical[2] frontiers defining pre- and postmaturity (MA = 259 days, MA = 294 days). The corrected frontiers in terms of the gestational age counted from "O" day, here referred to as conceptional age (CA), were calculated as follows: the limit for prematurity was obtained by subtracting from 259 the

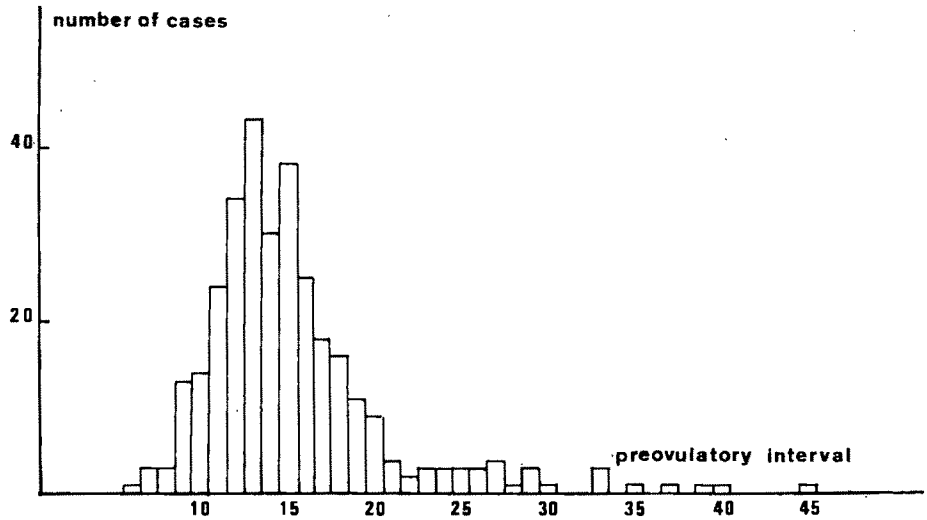


Fig. 1A. Distribution of interval between first day of LMP and last day of hypothermic phase: all births (317 cases).

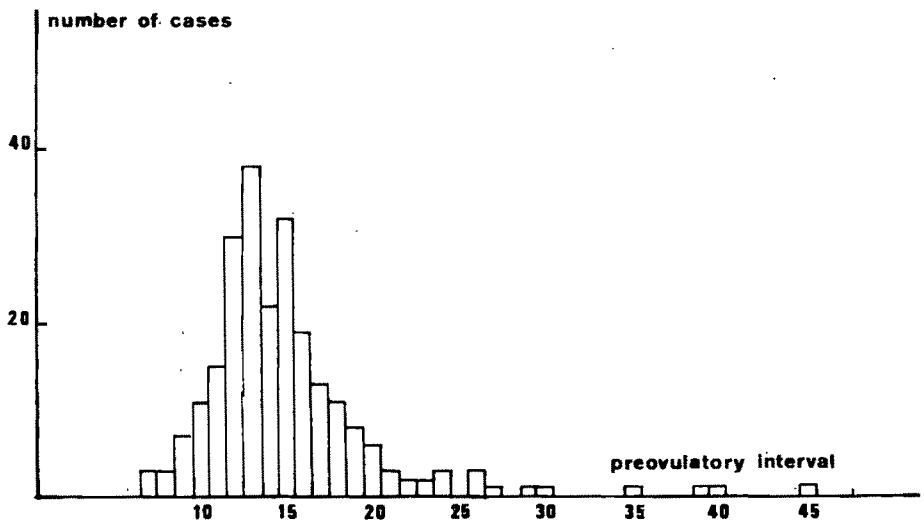


Fig. 1B. Distribution of interval between first day of LMP and last day of hypothermic phase: wanted births (239 cases).

equally classical[2] value: OI = 14. Hence the corrected frontier for prematurity is MA = OI + 245: a straight line of slope 1 and intercept 245. Similarly the postmaturity frontier is a straight line of slope 1 and intercept 294 − 14 = 280. The errors made in defining pre- and postmaturity on the basis of MA alone can hence be estimated by considering the distribution of the points in the zones numbered I to VI (Fig. 2) and are summarized in Table I.

The proportion of cases wrongly considered to be postmature according to MA—the only error rate estimated from reasonable numbers—is to be noted in particular: this proportion is quite considerable and amounts to nearly 70 per cent of all the cases classified as being postmature.

In addition, for the wanted births this error rate is 14/23 = 61 per cent and for the unwanted births 8/10 = 80 per cent. As for the other rates, the numbers involved are too low to allow a similar comparison to be made.

Furthermore, for the cases incorrectly classified as postmature, it is possible to estimate the order of magnitude of the error made: the menstrual age exceeds 294 days by a mean value of 5 days, whereas

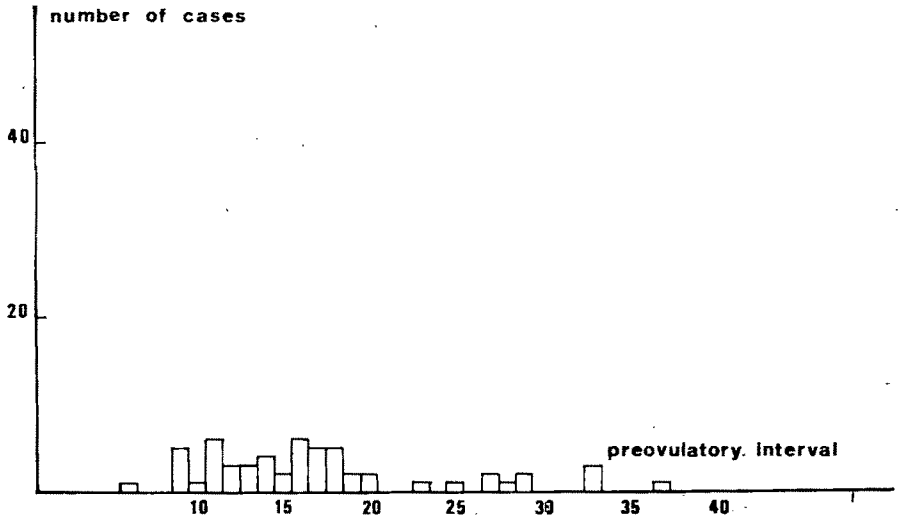


Fig. 1C. Distribution of interval between first day of LMP and last day of hypothermic phase: unwanted births (56 cases).

the mean conceptional age is 7 days below the corrected frontier value of 280. The total error is hence of the order of 12 days, and exceeds 1 week in 70 per cent of cases and 2 weeks in 30 per cent of cases. The most extreme case which corresponds to the highest OI value in Fig. 2 has a menstrual age of 312 days which greatly exceeds the MA postmaturity frontier of 294 (an excess of 18 days), whereas the conceptional age is well below the CA frontier of 280 (13 days). In this apparent case of extreme postmaturity the duration of gestation is quite normal and an error of 31 days was made in estimating the age of the fetus.

Finally, the proportion of postmatures which for our series was 11 per cent according to the classical definition, is 5 per cent under the new definition despite the addition of the undetected cases to those originally correctly classified. Furthermore, it can be seen in Fig. 2 that for the "true" postmatures the number of excess days with respect to the CA frontier of 280 is very small.

Comment

The results obtained require two justifications.

1. The conceptional age has been measured from "O" day, the exact time of fertilization being unknown. It is possible, however, to make an estimation of the importance of the error introduced by this approximation. The "O" day was determined by the authors in the same manner as for the present study for a further series of 70 cases which were obtained from Férin. The difference between "O" day and the day of maximum LH was 0.18 (S.D. = 0.06).[3] If, in agreement with Férin and associates,[4] one considers that ovulation occurs approximately 36 hours after the LH surge, and if further one admits that ovulation is followed closely by fertilization, then the delay between "O" day and fertilization can be neglected as a first approximation in comparison to the error committed when the variation in the preovulatory period is not taken into account.

Table I. Observed error rates associated with the classical definitions of prematurity and postmaturity

	Prematures	*Postmatures*
Incorrectly classified	$\frac{1}{16}\left(\frac{VI}{V+VI}\right)$	$\frac{23}{34}\left(\frac{III}{II+III}\right)$
Undetected	$\frac{3}{18}\left(\frac{IV}{IV+V}\right)$	$\frac{4}{15}\left(\frac{I}{I+II}\right)$

2. The new definitions of pre- and postmaturity are taken to apply to all women irrespective of their OI value. This implies that the duration of gestation counted from conception is independent of OI, a result which appears to be proved by the absence of any correlation between the two intervals.[5, 6]

If these two restrictions are accepted, then the present approach enables a direct estimation to be made of the error rates involved in considering gestation as starting at the last menstrual period. The estimated percentages of undetected postmatures (27 per cent) and prematures (17 per cent) as well as the proportion of incorrectly classified prematures (6 per cent) may be forwarded as no similar estimates appear to have been already reported in the literature, but with precaution as the numbers are low.

The percentage of incorrectly classified postmatures

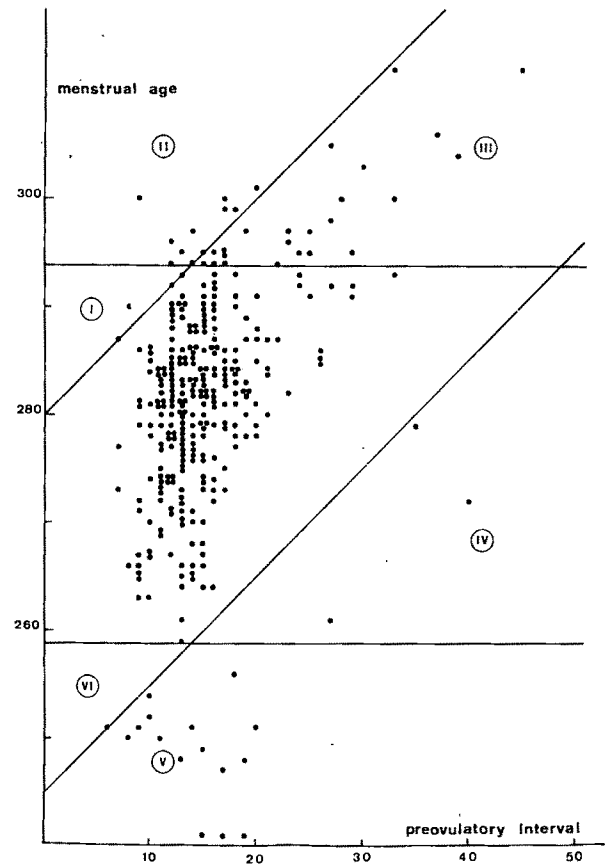


Fig. 2. Relationship between gestational age counted from the first day of the LMP and preovulatory interval.

merits greater attention. According to Saito and associates,[5] 70 per cent of the variation in the menstrual age of postmatures is explained by OI; this result is based on a consideration of the correlation between MA and OI which was calculated on a series of 110 women consulting for sterility. The present study was carried out on a larger series of women who may be considered to be more "normal" and, by a different and more direct method, estimates at once both the frequency of incorrectly classified postmatures, which is high, and the magnitude of the error made, which has a high mean value and may be quite considerable in certain extreme cases.

From the comparison of the wanted and the unwanted births, it appears, furthermore, that the risk of classifying as postmature an infant who is biologically at term, is greater for the unwanted than for the wanted births (80 vs. 60 per cent), this result being highly suggested by the OI distributions for the two groups. It hence follows that for any given population, the values of the risks will depend largely on the proportion of unwanted pregnancies, and also that even if menstrual age is corrected by the "usual day of ovulation," quite appreciable errors are likely to occur for these unwanted pregnancies.

If it was obvious *a priori* that any definition of postmaturity based on the date of the LMP should be corrected in order to take into account the variation of the preovulatory period, it was perhaps less easy to predict the full importance of this modification. The present estimates indicate that it is essential to bear this in mind before taking the decision to induce delivery or when an evaluation is to be made in a population of the postmaturity rate.

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The pattern and rates of metabolism of maternal plasma dehydroisoandrosterone sulfate in human pregnancy

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The present study was done to map the metabolic pathways and rates of maternal plasma clearance of dehydroisoandrosterone sulfate (MCR_{DS}) in pregnancy. In the present study, maternal plasma dehydroisoandrosterone sulfate (DS) metabolism was largely accounted for by two major pathways not present or not prominent in the nonpregnant woman. The first major pathway was clearance of maternal plasma DS by placental aromatization of DS to form estradiol (E2). This pathway accounted for approximately 35 per cent of the total clearance. The second major pathway of metabolism of maternal plasma DS was by 16α-hydroxylation within the maternal compartment. This pathway accounted for approximately 32 per cent of maternal plasma DS clearance. Two other minor pathways of DS metabolism, that is, loss to the fetus and excretion as unaltered DS into urine, accounted for less than 1 per cent of total metabolism in each instance. The final pathway of DS metabolism was excretion as neutral steroids such as urinary 17-ketosteroids and other undefined losses. By combining the rate of DS clearance (MCR_{DS}) from maternal plasma via all pathways with that fraction of DS removed uniquely by placental conversion of DS to estradiol (DS→E2), the placental clearance of DS→E2 ($PCDS_{E2}$) may be measured. The measurement of $PCDS_{E2}$ may be expected to reflect uteroplacental perfusion and as such may provide an investigative tool capable of assessing the dynamics of uteroplacental function in a variety of clinical conditions.

THE METABOLIC clearance rate of plasma dehydroisoandrosterone sulfate (MCR_{DS}) increases throughout the course of human gestation, such that the MCR_{DS} in the gravid woman may rise to 5 to 20 times that of the nonpregnant individual. In pregnancies compromised by neglected or advanced pregnancy-induced hypertension, however, the MCR_{DS} may be reduced markedly compared to that observed in normal pregnancy.[1, 2] In a prospective study in young primagravid women, the MCR_{DS} in early pregnancy was found to be greater in those women destined to develop pre-eclampsia than in those who remained normal. However, late in such pregnancies, the MCR_{DS} began to decrease even prior to the appearance of hypertension.[2] Since plasma dehydroisoandrosterone sulfate (DS) is utilized extensively by the placenta for estradiol (E2) formation, alterations in the MCR_{DS} in pregnancy may reflect changes in uteroplacental blood flow. On the other hand, since maternal plasma DS is metabolized through a variety of other nonplacental pathways, an alteration in clearance cannot necessarily be ascribed to a decrease in placental utilization since other routes of DS removal also may be altered. For this reason, a systematic study of the metabolic fate of DS via all routes of irreversible metabolism from maternal plasma was considered to be of signal importance.

The present study was designed to ascertain the rates of the various metabolic pathways of maternal plasma DS clearance in pregnancy. While it is well established

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Table I. Distribution of dehydroisoandrosterone sulfate (DS) metabolism in normal pregnancy

Patient	*Gestation (wk.)*	*DS→E2 (%)*	*DS→16-OHDS (%)*	*DS→DSu (%)*	*DS→Fetus (%)*	*DS→Neutral and other metabolites (%)*	*MCR_{DS} (L./24 hr.)*
G. W.	30		29.7				
M. T.	36	33.0	20.3	<1.0	<0.3	45.4	35.5
V. J.	36	35.4	23.5	<1.0	<0.3	39.8	55.2
S. W.	38	39.5	19.5	<1.0	<0.3	39.7	62.2
M. F.	38	29.0	41.3	<1.0	<0.3	28.4	44.7
B. C.	40	27.4	35.7	<1.0	<0.3	35.6	
L. H.	40		54.9				
M. H.	40	46.1					49.3
Mean		35.1	32.1	<1.0	<0.3	31.5	49.4

that DS is utilized extensively by the placenta for conversion to estradiol,[3] it has also been shown that considerable maternal plasma DS is converted to 16α-OH dehydroisoandrosterone sulfate (16-OHDS).[2,3] A similar metabolic pathway also is operative in the fetus where steroids are subject to extensive 16α-hydroxylation.[4] In fact, previous studies have shown that as much as 90 per cent of urinary estriol in pregnant women near term may be accounted for by the placental utilization of 16-OHDS of fetal origin.[3,5] Studies in these laboratories have shown that DS in maternal plasma, after undergoing 16α-hydroxylation in the maternal compartment, also is converted to estriol in the placenta.[3,6]

The present study was designed to quantify the rates of removal of maternal plasma DS by five separate metabolic pathways: (1) DS aromatization to E2 in the placenta, (2) 16α-hydroxylation of DS in the maternal compartment, (3) DS excretion into the urine unaltered, (4) DS transfer to the fetus, and (5) DS metabolism and excretion as neutral steroids other than 16α-hydroxy metabolites, e.g., the urinary 17-ketosteroids, androsterone, etiocholanolone, etc., and other undefined excretion.

In this study of women late in pregnancy, plasma DS metabolism was largely accounted for by two major pathways not prominent in the nonpregnant woman. The first major pathway was the clearance of DS from maternal plasma by placental aromatization of DS to form E2. This pathway accounted, on the average, for 35 per cent of the total clearance. Quantitatively, the second major pathway of metabolism of maternal plasma DS was by 16α-hydroxylation. This pathway, on the average, accounted for 32 per cent of maternal plasma DS clearance. Subsequently, 35 per cent of the 16-OHDS formed in the maternal compartment is converted to estriol in the placenta, while the remainder of 16-OHDS is further metabolized and/or excreted in the urine as neutral metabolites.[6] Very little maternal plasma DS reaches the fetus either as DS or as a metabolite thereof,[2] and the results of all studies to date are that less than 1 per cent of DS is excreted into urine as unaltered DS. The remainder of maternal plasma DS metabolism is attributed to other neutral pathways not involving 16α-hydroxylation.

The results of the present study show that in those instances in which the MCR_{DS} is markedly decreased during pregnancy, the decrease in clearance can be ascribed to decreases in the rates of one or both of two metabolic pathways, i.e., 16α-hydroxylation and/or placental aromatization of DS to form E2.

Materials and methods

The transfer constants of conversion of maternal plasma DS to E2, $[\rho]^{DSE^2}_{BU}$, and to 16-OHDS, $[\rho]^{DS16-OHDS}_{BU}$, were calculated on the basis of previously reported mathematical expressions and experimental designs.[2,3,7] Briefly, the transfer constant of conversion of maternal plasma DS to E2 was computed from the expression, $[\rho]^{DSE^2}_{BU} = Ri \div RE2u$, where Ri = the isotopic ratio of the injected tracers, ^3H-E2 and ^{14}C-DS, and RE2u = the $^3H/^{14}C$ ratio of urinary E2 (glucuronoside) isolated from a 3 to 5 day urine collection. The $[\rho]^{DS16-OHDS}_{BU}$ was measured as previously described,[2] and in a manner analogous to that for the transfer constant of conversion of DS to E2.[3,7] Following the intravenous injection of a tracer dose of ^{14}C-DS, ^3H-E2, and ^3H-16-OHDS, 16-OHD(S) was isolated from a 3 to 5 day urine collection. After extraction and solvolysis, purification of urinary 16-OHD was accomplished by gradient elution chromatography, thin-layer rechromatography and recrystallization with authentic carrier as described in earlier reports.[2,3,7] In these studies, urinary E2 also was isolated after β-glucuronidase hydrolysis. Thus in these studies the $[\rho]^{DSE^2}_{BU}$ as well as $[\rho]^{DS16-OHDS}_{BU}$ could be computed in the same study.

The excretion rate of DS into urine as DS was

Table II. Distribution of dehydroisoandrosterone sulfate (DS) metabolism in pregnancies complicated by hypertension

Patient	*Gestation (wk.)*	*DS→E2 (%)*	*DS→16-OHDS (%)*	*DS→DSu (%)*	*DS→fetus (%)*	*DS→Neutral and other metabolites (%)*	*MCR_{DS} (L./24 hr.)*
Pregnancy-induced hypertension (pre-eclampsia):							
D. T.	36	36.7	28.9	<1.0	<0.3	33.1	52.2
K. W.	37	31.9	26.9	<1.0	<0.3	39.9	35.6
Mean		34.3	27.9	<1.0	<0.3	36.5	43.9
Chronic essential hypertension:							
C. T.	24	23.0	23.9	<1.0	<0.3	51.8	22.9
S. W.	32*	7.3	52.0	<1.0	<0.3	39.4	60.3
L. M.	33	25.5	31.7	<1.0	<0.3	41.5	96.0
L. W.	34	27.7	31.7	<1.0	<0.3	39.3	54.7
M. K.	38	24.0	56.5	<1.0	<0.3	18.2	142.0
Mean		21.5	39.1	<1.0	<0.3	38.1	75.2

*Stillbirth 4 days after study completed.

calculated from data obtained from reverse isotope dilution studies following the addition of authentic ^{3}H-DS to an aliquot of the urine collection. Following extraction and solvolysis of that aliquot of the urine, dehydroisoandrosterone (D) was isolated, acetylated, and recrystallized to a constant $^3H/^{14}C$ ratio in successive mother liquors and crystals.

The extent of loss of plasma DS from the maternal compartment to the fetal compartment was calculated as described previously.[2] The fifth pathway of metabolism, i.e., the excretion of neutral metabolites and other unaccounted for metabolism, was estimated as that portion of the total metabolism not accounted for by the previously computed portions of metabolic removal.

The MCR_{DS} was calculated as previously reported[1, 2] and expressed as the liters of maternal plasma totally cleared of DS per 24 hours.

It is important to note that the dose of radioactivity administered to each of these volunteers* was 3μC or less. The radioisotope is stably incorporated into the steroid nucleus and its products are rapidly excreted into the urine. In fact, more than 50 per cent of the administered radioactivity appears in the maternal urine within 12 hours of administration. Additionally, recent studies have demonstrated that almost no radioactivity reaches the fetus.[2]

Results

The results obtained in the normal gravidas are presented in Table I. In those women, 36 to 40 weeks pregnant, the extent of maternal plasma DS converted to E2 averaged 35.1 per cent, and an average of 32.1 per cent of maternal plasma DS was converted to 16-OHDS. Less than 1 per cent of DS was excreted in the urine as DS (DS→DSu) in all women studied. Loss of DS to the fetal compartment in all studies was less than 0.3 per cent, and in many instances was so low as to be unmeasurable as previously reported.[2] The extent of DS removed from maternal plasma as neutral or other metabolites or by other routes of excretion sums a variety of metabolic pathways that are similar to those of the nonpregnant individual. These data are presented in Table I as the portion of DS clearance not measured by the other four pathways. This pathway includes the metabolism and excretion of DS as urinary 17-ketosteroids, e.g., androsterone and etiocholanolone, as well as other neutral steroids. These results are summarized and illustrated graphically in Fig. 1.

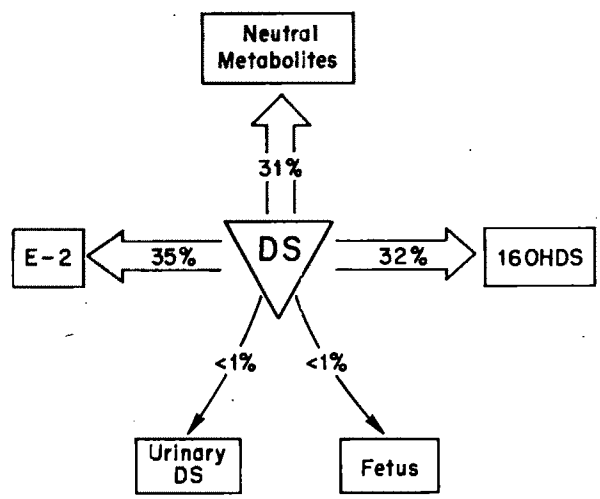


Fig. 1. The five metabolic pathways of dehydroisoandrosterone sulfate clearance from maternal plasma.

*Informed consent was obtained from all volunteers in this study.

Table III. Distribution of dehydroisoandrosterone sulfate (DS) metabolism before and after delivery and in a nonpregnant subject studied during the luteal phase of the menstrual cycle

Subject	*Gestation (wk.)*	*DS→E2 (%)*	*DS→16-OHDS (%)*	*DS→DSu (%)*	*DS→fetus (%)*	*DS→Neutral and other metabolites (%)*	*MCR_{DS} (L./24 hr.)*
M. K.	38	24	56.5	<0.1	<0.1	19.5	142
	3 days post partum	0	68.0				
	19 days post partum	0	36.0				
K. H.	Non-pregnant	0	16.5				

The metabolic clearance rates of maternal plasma DS were determined in five of these normal pregnant women between weeks 36 and 40 of gestation. The mean value for the MCR_{DS} was 49.4 L./24 hours, similar to that observed in normotensive, ambulatory, primigravid subjects late in gestation.[1, 2]

Two separate groups of gravidas with hypertension also were studied and these results are presented in Table II. Two women with pregnancy-induced hypertension were studied during weeks 36 and 37 of gestation. The extent of maternal plasma DS converted to E2 was 34.3 per cent and the extent of DS converted to 16-OHDS was 27.9 per cent, values similar to those observed in normotensive, ambulatory women at the same stage of pregnancy. As in the normotensive women, the amount of DS lost to the fetus and the amount of DS excreted unaltered in the urine was less than 1 per cent in each case. The mean MCR_{DS} was 43.9 L./24 hours for the two patients studied. Commonly, a decreased MCR_{DS} is observed in patients with advanced or neglected pre-eclampsia when compared to normotensive patients.[1, 2] Moreover, it has been observed that the MCR_{DS} continues to decrease in these hypertensive subjects until delivery or until a modified bedrest regimen is instituted.[1, 2, 8] In patient D. T. (Table II) the MCR_{DS} was measured after several weeks of modified bedrest, and for this reason may have been higher than that which otherwise would have been expected without the bedrest regimen.

The results of those studies in women with chronic essential hypertension also are presented in Table II. Importantly, these women also were studied while at modified bedrest. The extent of maternal plasma DS converted to E2 was 21.5 per cent in these subjects, a value somewhat lower than that observed in patients with pregnancy-induced hypertension at bedrest. However, it should be noted that the majority of these studies were carried out at an earlier stage of gestation than in the normotensive control subjects and in the subjects with pre-eclampsia. Interestingly, the extent of DS converted to 16-OHDS was 39.1 per cent in these patients with essential hypertension, a value which is greater than that found in both the normal and the pre-eclamptic patients even though the patients with chronic essential hypertension were studied at an earlier stage of gestation.

The mean MCR_{DS} was 75.2 L./24 hours in these women with essential hypertension, a value greater than that observed in both the pre-eclamptic and the ambulatory normotensive gravidas.

The smallest conversion of maternal plasma DS to E2 was observed in subject S. W. (Table II), whose fetus died 4 days after the completion of this study. Despite the small conversion of DS to E2 in this subject, the conversion of maternal plasma DS to 16OHDS (52 per cent) was not diminished, and the MCR_{DS} was still 60.3 L./24 hours.

To establish that the extensive 16α-hydroxylation of DS observed in the gravidas of this study was occurring in the maternal compartment, an additional study was performed and these results are presented in Table III. Patient M. K., with chronic hypertension, was studied during week 38 of gestation, again 3 days post partum, and then 19 days post partum. During week 38 of gestation, 24 per cent of maternal plasma DS was converted to E2 and 56.5 per cent was converted to 16-OHDS. The MCR_{DS} in this patient was 142 L./24 hours. Following delivery DS was no longer converted to estradiol, since this reaction is unique to the trophoblast. However, at this time (3 days post partum) there was an increase in the extent of conversion of plasma DS to 16-OHDS to 68 per cent. The increase in

the portion of total DS metabolism accounted for by this pathway likely occurred as the consequence of the removal of one rapid pathway of metabolism, i.e., the placental conversion of DS to E2. Nineteen days post partum there was again no conversion of plasma DS to E2 and the extent of DS converted to 16-OHDS had decreased to 36 per cent, suggesting that following delivery there is a slow loss in 16α-hydroxylating capacity. These findings suggest that the efficiency of 16α-hydroxylation within the maternal compartment is increased markedly during pregnancy. This view is further strengthened by the results of a study in K. H., a nonpregnant subject studied during the luteal phase of her ovarian cycle. In this woman there was no conversion of DS to E2 and only 16.5 per cent of plasma DS was converted to 16-OHDS.

Comment

The results of this study establish that there are two major, rapid routes of irreversible removal of DS from maternal plasma. These two pathways are either unique to or markedly increased in the pregnant state. The first of these pathways is the unique placental aromatization of maternal plasma DS to form estradiol. This pathway of metabolism accounts for an average of 35 per cent of the clearance of DS from maternal plasma in normal gravidas near term.

The second major rapid pathway of metabolism of maternal plasma DS is accomplished through 16α-hydroxylation within the maternal compartment. This pathway accounts, on the average, for 32 per cent of the clearance of plasma DS in late pregnancy. Moreover, the increased capacity for 16α-hydroxylation is lost slowly following delivery. This metabolic event, persisting transiently following pregnancy, is of considerable interest considering the relationship of age at the time of the first pregnancy[9] and of estriol formation to the possible genesis of breast carcinoma.[10]

Other routes of DS clearance from plasma during pregnancy include two minor pathways, i.e., the excretion of unaltered DS into the urine and losses to the fetus.

The remaining clearance of DS from maternal plasma can be attributed to neutral pathways that include metabolism to the 17-ketosteroids, e.g., androsterone and etiocholanolone, and other neutral products. This metabolic pathway accounts for 31 per cent of the clearance of DS from maternal plasma near term, whereas in nonpregnant subjects this mechanism accounts for the vast majority of DS clearance.

The results of the present study are consistent with the view that significant alterations in the MCR_{DS} during pregnancy result from alterations in either (1) the placental removal of maternal plasma DS by conversion to E2, or (2) the conversion of DS to 16OHDS in the maternal compartment, or both. Therefore, in order to interpret the metabolic particulars of a decrease in the MCR_{DS} occurring in any pathologic state of pregnancy, one must ascertain not only the total MCR_{DS} but the extent to which each of the major metabolic pathways is altered. Specifically, uteroplacental perfusion may be reflected by measuring that portion of the MCR_{DS} that is the consequence of the unique placental clearance of maternal plasma DS to estradiol. The data of such a specific computation is likely to reflect uteroplacental blood flow since significant reductions in placental enzymatic capacity have been demonstrated only rarely, e.g., in placental sulfatase deficiency.[11, 12] Furthermore, the transport of DS into the trophoblast is apparently dependent upon simple diffusion since earlier studies have shown that the extent of conversion of exogenously administered DS to E2 was independent of the amount of DS available for conversion, i.e., independent of the plasma DS production rate.[13]

The placental clearance of maternal plasma DS to estradiol ($PCDS_{E2}$) can be computed, and the measurement may be expected to reflect uteroplacental perfusion. The expression, $PCDS_{E2} = MCR_{DS} \times [\rho]^{DSE2}_{EU}$ represents that volume of maternal plasma uniquely and irreversibly cleared of DS by the placenta. For example, in subject S. W. (Table II), whose fetus died in utero after the study was completed, the placental clearance of DS by conversion to E2 was 3 ml. per minute, whereas the clearance rate of maternal plasma DS by conversion to 16-OHDS was 21.8 ml. per minute. On the other hand, in subject V. J. (Table I), the $PCDS_{E2}$ was 13.6 ml. per minute at 36 weeks' gestation, whereas the clearance rate of maternal plasma DS by conversion to 16ODHS was 9 ml. per minute.

With the use of these concepts a dynamic assessment of uteroplacental function in health and disease and during the evaluation of the pharmacologic effects of drugs administered to the gravid woman now can be accomplished by the specific measurement of the placental capability to clear maternal plasma of its DS content through the formation of estradiol.

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Venous distensibility during pregnancy determined by graded venous congestion

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The increase in volume of the human calf and forearm during pregnancy resulting from graded venous congestion has been measured plethysmographically in the raised leg and forearm of 10 recumbent subjects during and after pregnancy. Normal pressure volume curves were determined and the alterations in this curve over the various stages of gestation were presumed to indicate an alteration in the distensibility of the capacity blood vessels. This distensibility was found to increase with the progression of pregnancy in both the forearm and the calf particularly after the thirtieth week of pregnancy. The distensibility, however, appeared to return to below the 10 week gestation level at the eighth postpartum week. The increase in distensibility was greater in the calf than in the forearm although both were significantly increased.

THERE IS an increased incidence of varicose veins and thromboembolic disease during pregnancy.[1] Goodrich and Wood[2, 3] have also done a series of experiments at fixed graded venous congesting pressure of 30 mm. Hg where they found that there was increased venous distensibility during oral contraceptive therapy and they suggested that this increase in venous distensibility was associated with the loss of venous tone.

The investigations of McLennan[4] and Burwell and Metcalfe[5] on venous pressure during pregnancy showed that the varicosities during pregnancy were primarily due to interference with venous return by the enlarging uterus. They demonstrated quite conclusively that femoral vein pressure was higher during pregnancy than brachial vein pressures. This may be due in part to obstruction of venous return, from the legs by the enlarged uterus.[6] However, since varicosities may appear before much enlargement of the uterus has occurred, it is likely that relaxation of the veins may contribute to the condition.[7] This may explain the presence of dilated veins in the upper part of the body and that the general venous distensibility may be due to some physiologic process other than mechanical interference with the blood flow.

This investigation was designed to study venous distensibility in the calf and forearm at 10 week intervals throughout pregnancy and at 8 weeks after delivery. Venous distensibility was estimated by applying graded venous congestion to the limbs and measuring the resulting changes in calf and forearm volume.[8]

Methods

Experiments were carried out on 10 healthy pregnant females, from the tenth week of pregnancy. The patients were between 20 and 35 years of age and seven of them had not been pregnant before. Three had had one previous pregnancy and delivery. Subjects were studied at 10 week intervals and at 8 weeks after delivery. There was no history of varicose veins or thromboembolic disease in any of the patients.

The subjects rested for 20 minutes under standardized conditions, the room being thermostatically maintained at 22° C. The temperature of the plethysmograph was maintained at 34° C. for both the forearm and calf. The patient then lay on the couch in the supine position and the forearm and calf were fitted through the plethysmograph (Fig. 1). The right forearm and calf were held in a position 18 cm. above the heart level so as to reduce the contents of the low pressure capacity vessels.

Around the ankle and wrist pneumatic cuffs were

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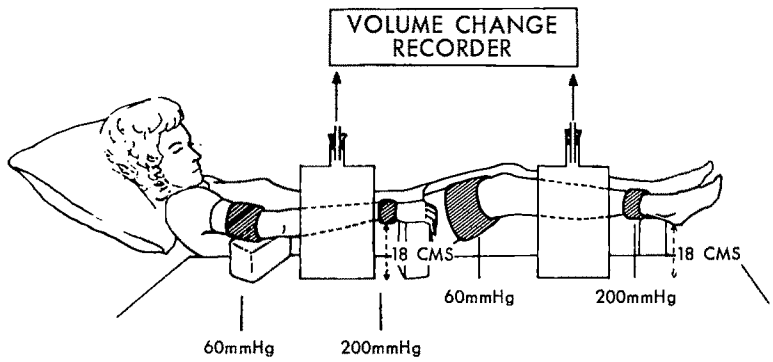


Fig. 1. Patient lying on couch under standardized experimental conditions.

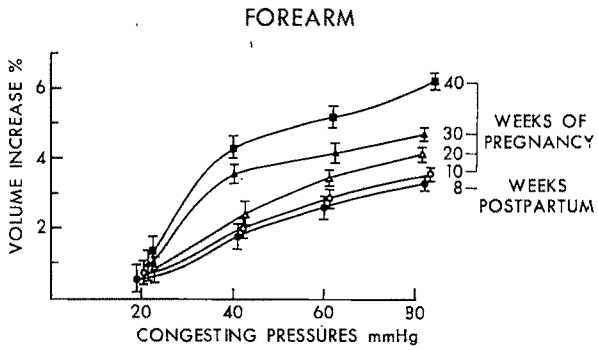


Fig. 2. The changes in forearm volume with venous congestion during and after pregnancy. Each symbol represents the mean of 40 observations on 10 women. The vertical bars represent one standard error of the mean.

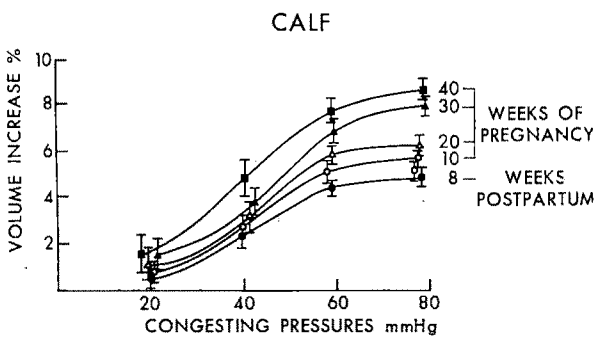


Fig. 3. The changes in calf volume with venous congestion during and after pregnancy.

inflated to 200 mm. Hg to arrest blood flow to the hand and foot when measurements of forearm and calf volume were being measured. The part of the limb enclosed in the plethysmograph was maintained under a nearly constant hydrostatic pressure and the pneumatic cuff proximal to the part was inflated by a large reservoir served by a foot pump at graded congesting pressures (10, 20, 40, 60, and 80 mm. Hg above atmospheric pressure). These were applied

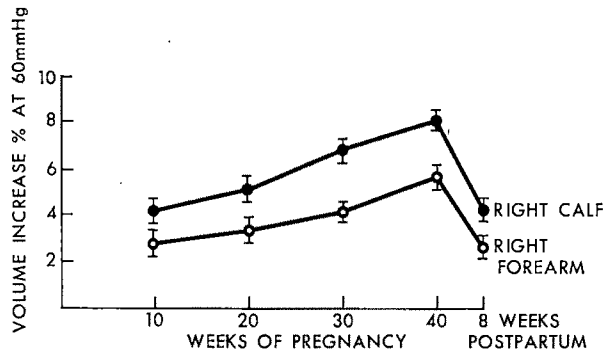


Fig. 4. A comparison of the volume changes in the forearm and calf throughout pregnancy with a congesting pressure of 60 mm.Hg.

successively for 2 minutes with 3 minute periods between each recording.[8]

The increase in volume at each congesting pressure was calculated by subtracting the resting volume from that reached after two minutes of congestion. The volume increase was expressed in milliliters per 100 of tissue and a pressure volume curves constructed. This was calculated at intervals of 10 weeks during the whole of pregnancy and at 8 weeks after delivery.

Results

Figs. 2 and 3 show the averaged results for all the experiments. The percentage increases in volume in the forearm (Fig. 2) and calf (Fig. 3) are plotted against the various congesting pressures at the different stages of pregnancy. As pregnancy progressed, venous congestion produced progressively greater percentage increases in both forearm and calf volume. The increases at the thirtieth and fortieth weeks of pregnancy to 40, 60, and 80 mm. Hg of venous congestion were significantly greater than those found with corresponding pressures at the tenth week of pregnancy. Eight weeks after delivery, the pressure-

volume curves had returned to about the tenth week of pregnancy values.

Fig. 4 compares the mean percentage increases in volume in the forearm and calf produced by a congesting pressure of 60 mm. Hg in all the subjects throughout pregnancy. Though both areas behaved similarly, the percentage increases in the calf were greater than those in the forearm.

Comment

When a congesting pressure is applied to a leg raised above heart levels, the volume of the calf increases as the previously collapsed capacity vessels fill up with blood. Eventually the venous pressure distal to the cuff exceeds the cuff pressure; blood then escapes under the cuff and a volume further increase is slight. This slight increase is due either to filtration of fluid into the tissue by the increased intravascular hydrostatic pressure or to the "slow give" of the capacity vessels. In these experiments the maximum size of the volume increase (i.e., the maximum increase) has been taken as an index of the distensibility of the calf and forearm blood vessels at that particular congesting pressure.

No measurements were made of the resting amount of blood in the calf or forearm, or of the alterations in this volume under the conditions studied. Since there were changes in blood flow through the calf and forearm during pregnancy, It is probable that the resting content of the calf and forearm did vary slightly. However, the contents of the low pressure capacity vessels were reduced as much as possible by elevating the limbs above heart level.

Furthermore these results would indicate that the loss of venous tone associated with pregnancy involves both the upper and lower extremities and is, therefore, not due merely to a "passive stretch" of the veins secondary to the increase in venous pressure in the lower extremities during pregnancy due to the enlarging uterus.[2] It is important to recognize that this method is independent of changes in total plasma volume or central venous pressure.

The mechanism responsible for the increase in venous distensibility would therefore appear to be general in nature. As was suggested by McCausland and associates[6] some circulating humoral factor of pregnancy may be involved and they had demonstrated that increased distensibility of the veins in the digit during pregnancy and in the luteal phase of the menstrual cycle occurs.

The results show that the distensibility of the calf and forearm capacity vessels increases as pregnancy progresses and falls after delivery. They do not indicate whether the increase in distensibility is due to the relaxation of the venous smooth muscle or to an alteration in the viscoelastic properties of the venous wall.[3] Though it is possible that the altered state of circulating hormones may be responsible for the changes,[6] the results do not exclude the possibility that this may also result from the release of vasoconstrictor tone.[10]

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The evaluation of Regionalized Perinatal Health Care Programs

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A survey, conducted in the summer of 1974, to determine the extent of regionalized perinatal care in the United States revealed 28 states to have programs in operation. Evaluation was a common concern of these programs. A model for the evaluation of Regionalized Perinatal Care Programs is presented here with the North Carolina program used as an example. Evaluation was mandated as an integral component of the program in North Carolina, and this model has been developed in response to that mandate.

IN RECENT YEARS, the concept of regionalization of perinatal health services has become increasingly popular as a clinical and public health approach toward improving perinatal care. In order to determine the actual extent of Regionalized Perinatal Care Programs (RPCP's), a nationwide survey was conducted in the summer of 1974.

A brief questionnaire was sent to the Director of Maternal and Child Health in each of the 50 states, Washington, D. C., and New York City. Included was a covering letter defining the minimum requirements of regionalized perinatal care as: (1) identification of high-risk pregnancies to allow for delivery in hospitals designated as regional centers that are organized for optimal obstetric and newborn care; (2) identification of high-risk newborn infants and transportation, where appropriate, to those regional hospitals staffed, equipped, and organized for neonatal intensive care. All questionnaires were completed and returned (Table I). Operating programs were reported in 28 states, 15 of these on a statewide basis. Evaluations of operating programs were either in progress or planned for 26 states. Further, 16 states indicated plans to implement a program within the next two years, including evaluation of their efforts. Only four states reported no plan for regionalization of perinatal care by 1976.

The status of many of the operating programs and a review of the development of regionalized perinatal care has been presented elsewhere.[1] In contrast, little published information is available which describes the impact of regionalized perinatal care on perinatal outcome. In those reports which are available, certain methodologic problems make interpretation of the results difficult. For example, neonatal mortality rates have been reported to decline more rapidly in the years following implementation of neonatal intensive care units than in the immediately preceding years in Wisconsin[2] and Colorado.[3] However, since the mortality experience of control populations unaffected by the programs was not studied, it cannot necessarily be concluded that the reductions in the mortality rate were attributable to the effects of the RPCP's in those states. On the contrary, after approximately a decade of slight change in infant mortality rates, ending in the mid-1960's, declining infant mortality rates have been observed throughout the country since the late 1960's.[4]

During the first three years of operation of the neonatal intensive care unit in Arizona, the fatality rate per 100 infants with the respiratory distress syndrome was 32 among infants transported to the regional centers compared to 59 for those who were not transported.[5] Although these results are encouraging, the possibility that they may be due to selection bias

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Table I. Summary of reported status of state RPCP's, August, 1974

Evaluation	*Program operating*		*No program operating*		Total
	Program operating statewide	*Program operating but not statewide*	*Program planned*	*No program planned*	
In progress	3	4	–	–	7
Planned for future	11	8	16	–	35
None	1	1	4	4	10
Total	15	13	20	4	52

Table II. Perinatal mortality rates by category of hospital, birth weight, gestation, and race: North Carolina, 1970 through 1972

Birth weight	*Five hospitals*		*Other hospitals*	
	≤34 weeks' gestation	*≥35 weeks' gestation*	*≤34 weeks' gestation*	*≥35 weeks' gestation*
≤2,000 grams				
White	613.1 (168/274)	283.0 (30/106)	559.8 (2,270/4,055)	306.5 (476/1,553)
Nonwhite	513.6 (397/773)	239.1 (66/276)	495.0 (1,492/3,014)	273.6 (252/921)
≥2,001 grams				
White	69.7 (20/287)	10.4 (104/10,026)	55.6 (283/5,087)	9.7 (1,740/178,558)
Nonwhite	27.6 (32/1,160)	9.6 (188/12,247)	34.0 (179/5,265)	12.8 (744/57,945)

By applying the lowest rates in each race–birth-weight–gestation category, an estimated reduction in the total perinatal mortality rate of 4.0 per cent is obtained.

cannot be ruled out, and in the absence of detailed description of the two populations one cannot determine whether or not they were of comparable risk.

The report of the Perinatal Mortality Committee of the Province of Quebec[6] is of particular importance because of the adequacy of controls in the analysis. Among infants born in 1967 through 1969 in hospitals registering more than 1,000 deliveries annually, the perinatal mortality rate per 1,000 was lowest in hospitals with intramural neonatal intensive care units (14.7), followed in ascending order by hospitals without neonatal intensive care units but which referred infants to the regional centers (16.9), and hospitals which provided neither intramural nor referral neonatal intensive care (19.1). The same pattern prevailed for both fetal and neonatal mortality rates, with the latter controlled for birth weight of the infant (1,000 to 2,500 grams and more than 2,500 grams). This is the most persuasive report to date from a methodologic viewpoint documenting the association between regionalized perinatal care and declining perinatal mortality rates, even though nonrandom selection of patients for different hospital categories may have resulted in neonatal risk which varied in unknown ways.

Background of the North Carolina RPCP's

In October, 1973, the Task Force on Maternal-Infant Care of the Governor's Council on Comprehensive Health Planning issued a report which recommended regionalization of perinatal health services in North Carolina.[7] This recommendation was based in part on the fact that in 1969, the most recent year for which national perinatal mortality data were available, only seven states had crude perinatal mortality rates exceeding the rate reported for North Carolina. In 1972, a total of 89,318 live births, 1,321 fetal deaths (at 20 weeks' gestation or more), and 1,474 neonatal deaths (occurring within 28 days of birth) were registered in North Carolina, for an over-all fetal mortality rate of 14.6, neonatal mortality rate of 16.5, and perinatal mortality rate of 30.8 per 1,000.[8]

The Task Force Report recommended voluntary certification of three levels of hospitals which would be capable of providing different levels of sophistication of obstetric and neonatal care. The program calls for

Table III. Perinatal mortality rates* by category of hospital, birth weight, gestation, and race: North Carolina, 1970 through 1972

Birth weight	*Five hospitals*		*Other hospitals*	
	≤34 weeks' gestation	*≥35 weeks' gestation*	*≤34 weeks' gestation*	*≥35 weeks' gestation*
≤2,000 grams				
White	593.0 (118/199)	265.8 (21/79)	551.8 (1,709/3,097)	300.4 (368/1,225)
Nonwhite	500.0 (298/596)	216.7 (44/203)	487.9 (1,231/2,523)	283.7 (223/786)
≥2,001 grams				
White	57.7 (12/208)	10.5 (82/7,809)	55.3 (220/3,980)	9.5 (1,344/140,883)
Nonwhite	17.4 (16/921)	9.4 (92/9,802)	32.2 (143/4,447)	12.7 (607/47,979)

Reduction in perinatal mortality rates by applying lowest rate in each category = 5.2 per cent.
*Deliveries occurring outside the mother's county of residence are excluded.

dividing the state into six regions in each of which approximately eight Level I hospitals would provide uncomplicated obstetric and neonatal care for an estimated 85 per cent of expectant mothers and babies; two Level II hospitals would receive referrals from Level I hospitals for more complicated cases, accounting for 11 per cent of the births; and one Level III hospital would provide the most specialized obstetric and neonatal services, including neonatal intensive care, required for the remaining 4 per cent of the population. The Level III hospital would also assume responsibility for ongoing education and the over-all quality of care within the region. In addition to providing care for the high-risk patients referred for care, Levels II and III hospitals would provide routine care for the patients residing within the immediate geographic area. In response to the Task Force Report, the General Assembly of North Carolina approved legislation authorizing funding for one year for the program to be initiated at one facility of each of the three levels and directed that evaluation of the program be undertaken.[9]

Predicted effect of RPCP's on perinatal deaths in North Carolina

Predictions of the effect of RPCP's on perinatal deaths in North Carolina indicated that 30 to 50 per cent of perinatal deaths are preventable in theory.[7] However, analysis of North Carolina's vital statistics suggests that the above predictions of reduction in mortality rate may take several years to achieve, and targets for the early stages of the program should be less ambitious. Perinatal mortality rates controlled for race, birth weight, and length of gestation are shown in Table II for five hospitals* which have had the most specialized obstetric and neonatal services in the state and thus approximate Level III hospitals, compared to rates in all other hospitals. Within each race–birth-weight–gestation group, the rates were approximately the same regardless of where delivery occurred. The lowest rate within each group may be taken as a realistic target for the early stages of the program. When these lowest rates are applied to the total population at risk, an estimated 4 per cent reduction in the perinatal mortality rate is obtained. It is appreciated that this calculation does not take into account additional reductions in perinatal deaths that may accrue to patients cared for in the Level III hospitals when the complete RPCP is implemented. This estimate also does not account for differences in medical characteristics of the populations in the two groups of hospitals. However, since most of the medical conditions which can be treated successfully by intensive neonatal care are directly associated with low birth weight and/or preterm delivery, controlling for birth weight and length of gestation should minimize this potential bias.

The effect of bias resulting from referral of high-risk patients to the "five hospitals" from other communities may be reduced further by excluding from analysis the patients who were delivered in hospitals outside the mother's county of residence (Table III). In this case, the reduction in the perinatal mortality rate is 5 per cent when the lowest rate in each group is applied to the total population, slightly larger than before.

*Baptist, Charlotte Memorial, Duke, North Carolina Memorial, and Wake County Memorial Hospitals.

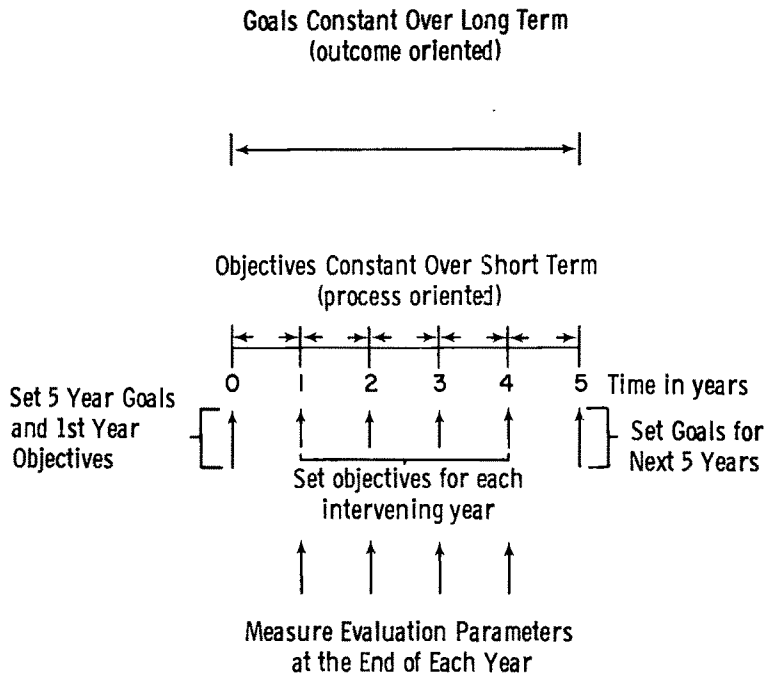


Fig. 1. Model for measurement of goal fulfillment.

Although the effect of medical risk cannot be directly controlled in analyzing currently available perinatal mortality data, this does not appear to invalidate the above results since it has been suggested previously that less than one per cent of variance in the infant mortality rate can be attributed to medical risk factors alone when birth weight is eliminated as an independent variable.[10]

These calculations indicate practical targets in regard to reduction in perinatal deaths for which the program should aim during its early years. Theoretical calculations show what may be possible with modern medical technology, and these will serve as long-range targets toward which the program will step in small increments.

The evaluation plan

The legislation authorizing North Carolina's program mandated evaluation as an integral component. The evaluation plan will permit an accurate assessment of the extent to which any changes observed in perinatal deaths and morbidity are due to the program itself. Furthermore, since it may be premature to establish final criteria by which success or failure of the program are to be judged, the evaluation plan should be flexible. Thus, it will be possible to measure achievement of objectives as they may change from year to year, which is likely to happen as this new program accumulates experience. Finally, the evaluation should be designed not only to determine whether the program did or did not reduce perinatal morbidity and deaths but also to study the processes by which regionalized perinatal care is supposed to lead to the desired improvements in perinatal outcome.

The evaluation methodology presented in the remainder of this report satisfies the above criteria and is a model which was developed for the use of the North Carolina RPCP evaluators. This methodology has been applied successfully to other health service programs.[11] By measuring not only the accomplishment of desired outcomes but also the performance of specific processes aimed at attaining the desired outcomes, this methodology can assist in program planning and management as well as determine the impact of regionalization of perinatal care. The details presented in the following sections serve to illustrate the methodology of this evaluation scheme.

The basic concept of the proposed evaluation design is that the program will move in small steps toward achieving its desired long-range outcomes (goals). The type of work (activity) and the amount of that work to be performed by a certain date (target) constitute an objective, and the totality of objectives at any one time determines the step. The longer-term, outcome-oriented goals, which remain fairly constant over, say, a five-year period, are set at the beginning of the

program. The shorter-term, process-oriented objectives are determined more frequently (e.g., yearly) and work toward the long-term goals. Thus, the objectives defined for any stage in program development are based on the progress achieved in preceding steps. The basic concept of the proposed evaluation methodology is illustrated in Fig. 1.

The parameters of evaluation

Quantitative measures will be made of the following parameters: (1) the degree to which objectives are fulfilled (achievement), and (2) the degree to which goals are attained (effectiveness).

The statistical methods used to measure these parameters have been described in detail previously.[11] In brief, a numerical score (achievement index) is assigned to each objective, based on one of a number of alternative scoring devices. In the early stages of the program, simple "yes" or "no" measures of achievement will be most practical. After the program is implemented and as activities and targets become more precisely defined, more refined measures of achievement can be made.

Achievement can be measured for a specific objective, for a range of related objectives, and for the entire program by taking appropriate weighted averages of the achievements for individual objectives. Over-all program achievement may be determined yearly, thus providing necessary information for annual reports to the legislature. Achievement will be measured for individual regions and hospitals, with appropriate feedback of information to these sources. It must be emphasized that objectives are set by the program policy makers and administrators, and these are translated into measurable terms by the evaluators. This ensures that the evaluation effort is an integral part of the program.

Effectiveness is measured relative to long-term targets of the program, in contrast to achievement which is relative to a short-term, intermediate target. Effectiveness either can be measured directly, as in the case of an outcome variable (e.g., reduction of the perinatal mortality rate) or can be indicated indirectly by the achievement scores. The latter technique would be more appropriate for a process-oriented goal area, such as Goal I as shown in the next section, i.e., to initiate and maintain the program as an operating unit.

The degree to which the regionalization program can be determined to be the cause of a change in perinatal morbidity and mortality rates and through which processes is dependent upon the proper selection of controls. Whether a causal association exists between the program and any changes in morbidity and/or mortality rates which may occur could be conclusively demonstrated on the basis of a prospective intervention study in which patients are assigned at random to treatment (regionalized perinatal care) or control (standard perinatal care) groups. Despite the benefit which would accrue to establishing such information, as with most health service programs, it was not considered feasible to institute a randomized study. However, an alternative was accepted which will permit limited demonstration of a cause-and-effect association between the program and improvement in pregnancy outcome, i.e., identification of a control group of patients receiving standard perinatal care in a region where the program has not been implemented. However, this quasiexperimental design will not eliminate the effects of bias due to patient selection, but it does represent a significant advance over studying the program's effects on only patients receiving the new services without any control group.

An example of the methodology applied to the North Carolina program

On the basis of the Task Force Report,[7] the following goals have been selected as preliminary to stating the detailed activities: (1) initiate and maintain the program; (2) enroll the hospitals into the program; (3) deliver high-quality hospital care; (4) deliver high-quality prenatal and interconceptional care; (5) educate physicians providing perinatal care to utilize the program; (6) promote consultation, referral and transportation between various levels of hospitals in a region; (7) reduce perinatal morbidity and mortality rates.

These seven goals are arranged in an approximately progressive sequence and represent the long-term aims of the program. The health-status outcomes of interest are specified in Goal 7, while the series of processes needed to bring about these outcomes are indicated by the first six goals. The program will work toward fulfilling the goals in small steps, with each step corresponding to the detailed objectives relevant to the stage of program development that exists at the time.

For the purposes of illustration, sample objectives (activities and targets) and planned resources are shown for the second and third goals in Tables IV and V. Each of these objectives may be measured by simply scoring whether the target was achieved. The average score within a goal will indicate the degree to which the processes within that goal are being carried out. On the basis of performance during the first year, new targets will be established for the second year.

Table IV. Goal 2: Enroll hospitals into the program (Region 1)

Objective		*Resources planned*	*Weight*
Activity	*Target*		
1. Inform hospitals of the program	All hospitals informed of program by November 1, 1974	Two secretarial days—mail information statement	3
2. Establish criteria for certification of hospitals	Criteria established by December 1, 1974	Two weeks—Advisory Committee Director's time	3
3. Establish mechanism for certification of hospitals	Mechanism established by December 1, 1974	One week's time—State Director	2
4. Identify one hospital at each of three levels for certification	Three hospitals identified by December 15, 1974	Two week's time—Advisory Council and Administrator of each hospital	2
5. Certify three hospitals in region	Three hospitals certified by January 1, 1975	Two week's time—Advisory Council and Director	4
6. Determine amount of renovation required in each hospital	Amount determined for three hospitals by January 15, 1975	One week per hospital—Review Committee of Advisory Council	3
7. Establish criteria for approving renovation required in certified hospitals	Official criteria established by January 31, 1975	?	3
8. Approve renovations required in each certified hospital	Approve renovations by January 31, 1975	?	1
9. Renovate each hospital as required	Each hospital ready to receive patients by April 1, 1975	Eight week's construction	4
10. Develop standards for consultation-referral among hospitals	Written standard developed and distributed to physicians at hospitals by April 15, 1975	One month's time—Regional vs. State Council	3
11. Implement system of consultation-referral among hospitals meeting above standards	Consultation-referral system operative by April 15, 1975	Two week's time—Regional Council	5

Weights may be allocated to objectives to indicate their relative importance within each goal. For example the highest-priority objectives may be given a weight of 5; the next highest, 4; and so on. Then weighted averages of achievement scores may be computed. This represents a refinement over the computation of straight averages. To illustrate these simple calculations, suppose the priorities of the first-year objectives for goals 2 and 3 were as indicated in the weight column. Suppose further that in Table IV the first five and last two targets were reached and the middle four were not. Score unity if the target was reached and zero otherwise. The over-all achievement for Goal 2 then may be calculated as follows:

$$\text{Achievement} = \frac{\text{weighted sum of scores}}{\text{sum of weights}} = \frac{3 \times 1 + 3 \times 1 + 2 \times 1 + 2 \times 1 + 4 \times 1}{3 + 3 + 2 + 2 + 4} \frac{-3 \times 0 + 3 \times 0 + 1 \times 0 + 4 \times 0 + 3 \times 1 + 5 \times 1}{+ 3 + 3 + 1 + 4 + 3 + 5} = 22/33\ (0.67).$$

A score of 0.67 or 67 per cent would represent the degree to which the goal processes were fulfilled, given the stage of program development that existed. More refined scoring devices may be developed to measure goal fulfillment more accurately.[11]

However, the above calculations are only a guide to over-all program effectiveness. The program is only

Table V. Goal 3: Deliver high-quality hospital care

Objective		*Resources planned*	*Weight*
Activity	*Target*		
1. Develop standards of education for health-care providers as recommended in Task Force Report	Standards developed by April 1, 1975	Two to four weeks—Advisory Council and Director	3
2. Conduct educational activities in participating hospitals according to above standards	Educational activities initiated by April 1, 1975	?	4
3. Employ additional personnel in each participating hospital as recommended in Task Force Report	Personnel hired by by April 1, 1975	Two weeks—Hospital Administrator, Dept. Chairman	3
4. Develop standards of perinatal care (hospital care standards by ACOG and ambulatory care standards by APHA may be adopted)	Standards developed by March 1, 1975	Statewide Advisory Committee—develop own standards or adopt national Task Force standards	3
5. Establish regional Perinatal Mortality Committees	Committee established in Region 1 by January 1, 1975	Three days—Regional Advisory Council time	2
6. Review every perinatal death in each region	Every perinatal death	One Perinatal Committee day/15 deaths (each region will have 300 to 320 per year)	5
7. Determine "avoidable" factors for each death and % of preventable deaths	Every perinatal death	One perinatal Committee day/15 deaths	4
8. Feedback information regarding preventability of deaths to providers of care	All providers involved participate in review conference and/or receive report	?	3
9. Follow performance of above on statewide basis for one or two tracer conditions (e.g., birth weight < 2,000 grams, diabetic mothers and newborn infants)	Monitor delivery of care for all infants with specified tracer conditions	?	3

really effective if it has some measurable effect on health outcomes. It is essential that one or more goals are stated in terms of desired outcomes and that these outcomes are monitored directly. Here, Goal 7 indicates the major outcomes of concern. The precise areas of morbidity that are to be measured must be defined and then adequate data must be collected to monitor the outcomes. The achievement scores are merely indicators of program performance, whereas the outcomes are true measures of effectiveness.

The "tracer" conditions method proposed by Kessner and associates[12] will be used to measure the impact of the program on perinatal morbidity. These measures will, in part, determine the effectiveness of the program. Listed in order of importance, tracer conditions must: (1) have a definite functional impact on health status; (2) be relatively well defined and easy to diagnose; (3) have prevalence high enough to permit the collection of adequate data from a limited population sample; (4) have a variation in the natural history of the condition, based on utilization and effectiveness of medical care; (5) have well-defined techniques of management for at least one of the following processes—prevention, diagnosis, and treatment; (6)

include a relatively clear understanding of the effects of sociocultural, economic, behavioral, and environmental factors on the condition.

In the context of a broadly conceived perinatal health care program, tracer conditions could be selected from the full spectrum of the reproductive cycle, i.e., preconceptional, prenatal, intrapartum, neonatal, postpartum, and interconceptional periods. For example, with regard to preconceptional and interconceptional conditions, the incidence of pregnancy or childbearing among girls under 17 years of age would qualify as a tracer condition. Prenatal medical conditions such as anemia, pyelonephritis, toxemia of pregnancy, diabetes, and hypertension are illustrations of maternal tracer conditions. Placenta previa, premature separation of the placenta, prolonged labor, and breech delivery are intrapartum examples. Low birth weight and short gestational age as well as respiratory distress syndrome and five-minute Apgar score less than 7 are neonatal tracer conditions. Examples of tracers for long-term measures of perinatal morbidity would be neurological damage and intellectual deficit at one and three years of age among children whose birth weights were <1,500 grams or those who were infants of diabetic mothers.

It must be re-emphasized that a control population is required to assess adequately the impact of the program on perinatal morbidity. Hence, similar outcome data must also be collected for the control region in order to assess whether changes in perinatal morbidity and mortality rates are, in fact, related to the program or to other extraneous factors. If there were changes in morbidity and mortality rates in the project region and similar changes were noted in the control region, then it would not be reasonable to conclude that the program was responsible for observed differences. However, if greater changes were observed in the project region than the control region, then it would appear reasonable to conclude that the program has some effect on morbidity and mortality rates.

Comment

The national survey to determine the extent of regionalization and evaluation efforts in operating or planned programs showed that RPCP's are in operation or planned for virtually the entire nation, and most of the programs are engaged in or propose evaluation.

In view of these findings, it seemed especially timely to describe the evaluation design being implemented in North Carolina. It will provide for planning and management requirements. Achievement of program goals and objectives that are developed by the program administrators will be fed back as the RPCP progresses. Data will be collected and processed so that the health administrators and legislators who monitor program performance can be presented with objective evidence of goal attainment.

A control region is essential in determining the effect of RPCP on perinatal mortality and morbidity rates. The authors are confident that a population can be studied in a region of the state not participating in the RPCP. Therefore, if improvements occur in the study region, there will be much less likelihood that questions will be raised regarding whether they were produced by the program or other concurrent factors.

It is estimated that about two years of program operation will be required in a region with about 1,400 births per year, even if the perinatal mortality rate is as high as 35 per 1,000, before an impact as great as a seven-point reduction in the perinatal mortality rate will be demonstrable. A longer period of follow-up probably will be necessary to establish a clear relationship between RPCP and tracer-condition measures of perinatal morbidity such as those suggested earlier.

In view of the current national interest in RPCP's and the large amounts of resources about to be invested, vigorous evaluation of regionalized perinatal care is required. One particular approach to evaluation which is being implemented in the North Carolina program has been presented here. The findings of the described evaluation will be the subject of future reports and hopefully will stimulate responses from other programs.

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Regionalization of a birth defects prevention clinic

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Screening programs to detect the carrier state of Tay-Sachs disease have been established in many large urban areas. A regionalized program has been established in the middle-Tennessee area to permit smaller communities to benefit from such programs. The numerical and psychosocial results of this program are discussed. The general concept of regionalization of health care delivery as related to birth defects screening programs is presented. Through such regionalized programs, obstetricians may be provided with new information concerning diagnostic and screening tests for genetic diseases.

IN 1971 THE first community-wide voluntary genetic screening program for the asymptomatic heterozygote carrier of the Tay-Sachs gene was initiated in the Baltimore-Washington area.[1] Individual institutions in other large cities have subsequently performed Tay-Sachs screenings. We have applied the concept of regionalization of medical care to the genetic screening for Tay-Sachs disease and have demonstrated that mass screening is feasible for less densely populated areas of the country.

Tay-Sachs disease is a rare, fatal, autosomal recessive disease, predominantly affecting Jewish infants. Symptoms become evident between 3 and 6 months of age. Progressive mental and physical deterioration ensues, and death occurs by 3 to 5 years of age. The syndrome is associated with an accumulation of a lipid (ganglioside GM_2) in nerve cells, due to the absence of a specific cleaving enzyme, hexosaminidase A. Diminished levels of this enzyme have been found in the serum of parents (obligate carriers) of children with Tay-Sachs disease. It is estimated that 1 in 24 Jewish people of Central European ancestry are carriers. The carrier rate in the non-Jewish population is approximately one in 300.[1]

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Methods

A regionalized Tay-Sachs disease screening program for the tricity (Nashville-Knoxville-Chattanooga) area of Tennessee was undertaken by the Vanderbilt University Birth Defects Prevention Clinic, Nashville. The clinic's professional staff consisted of an obstetrician, a mental health clinical specialist, and a geneticist.

Detailed protocols established by Dr. Michael Kaback and the California Tay-Sachs Disease Prevention Program to effectively educate and voluntarily screen small communities were followed as described below. Community approval for the program was obtained from religious, lay, and medical leaders at an initial educational and organizational community meeting. Qualified and interested physicians were identified and enlisted to conduct prescreening educational meetings and postscreening retesting and counseling. Other health professionals in the area were notified of the impending program by letters from these designated local physicians. Responsibility for publicity and educational campaigns was delegated to Jewish Community Center and rabbinical leaders. Expensive publicity was not necessary. Synagogue and community center mailing lists included the names of almost every identified Jewish person. Letters, brochures, and notices of educational meetings were disseminated. Sermons and speeches to women's groups by religious and lay leaders were found to be the most effective means of reaching the population. Local radio, television, and newspaper facilities were used sparingly to reach other nonidentified Jewish individuals.

The screenings, supervised by the clinic staff, were conducted in one or two evening sessions at each city's local Jewish Community Center. Doctors and nurses from the community volunteered to draw the blood

Table I. Results of regional Tay-Sachs screening

City	Estimated total Jewish population*	Tested		Identified		Couples at risk
		No.	%	No.	%	
Nashville	3,200	304	9	14	4	0
Knoxville	1,500	140	9	3	2	0
Chattanooga	2,500	150	6	8	5	1
Total	7,200	594	8	25	4	1

*Jewish Welfare Board Yearbook—1973, published by the National Jewish Welfare Board, New York, New York.

samples. Additional technical details of Tay-Sachs screenings have been published elsewhere.[2]

Serum and white blood cell preparations were processed at Vanderbilt University and mailed to the California Tay-Sachs Disease Prevention Program for final enzyme analysis. Results were available within 3 to 4 weeks. Counseling and retesting for inconclusive results were performed by designated medical authorities in the individual communities. Questionnaires were utilized to evaluate the educational program and the psychosocial affects of the screenings.

After the mass screenings and counseling had been completed, community leaders were asked to continue the testing on an as needed basis. Rabbis incorporated information about Tay-Sachs disease in their premarital counseling sessions. Testing information was included in the packets given to new couples entering the community by various community organizations. Medical authorities in each community were asked to be prepared to continue to send small numbers of specimens to the California laboratory for evaluation.

Results

The total Jewish population for the entire region was estimated to be 8,500. Compliance rate and number of identified carriers are summarized in Table I. The numerical results are similar to results from initial screenings in other cities.[1, 2] Twenty-five carriers and one couple at risk have been identified at the initial screenings. The carrier status of relatives of identified carriers is presently being evaluated here and at other centers.

The psychosocial aspects of the screening were also evaluated. Specific details relating to compliance factors, anxiety within a community, confidentiality, and educational programs are discussed below. Questionnaires returned by participants at the screenings revealed that older couples, beyond the childbearing age, wished to be screened for the information they could give to older children in other cities. Couples beyond the child-planning years participated to give genetic information to their siblings. Single mature individuals, including older teenagers, participated because they wished to know more about themselves. We noted, as did Kaback,[2] that young couples, planning future children, had a direct and immediate incentive for participating in the screening programs. We do feel, however, that it is appropriate to attempt to screen individuals other than young married couples.

It has been noted that anxiety is created within a community undergoing screening. Publicity for the program may promote, in some, the feeling of immediacy of danger. This "psychic burden" has provoked medical authorities in one city to negate the value of the screening.[3] Specific efforts were made to scrutinize for and deal with this type of anxiety reaction. It was noted that individuals in small communities felt free to consult with program leaders who were well known and accessible to them. Anxiety within the community could then be quickly allayed.

The confidentiality of the information obtained and the fear of the future use of this genetic information, by an as yet unspecified data collection agency, was of concern to many people. Although the importance of the accumulation of scientific data has been acknowledged, individual project directors must offer some guarantee of confidentiality to the community at the outset of the genetic screening program. People also wished to be assured that only the diagnostic test for the Tay-Sachs carrier state would be performed on their blood. They were unwilling to expose themselves without prior educational programs to other tests.

A disappointing result of the program was our unsuccessful educational campaign. We confirmed the findings of Beck, Blarchman, and Scriver[4] and Gordis[5] that participants in Tay-Sachs screening programs often did not understand the medical-genetic facts of Tay-Sachs disease, nor did they fully understand the reasons for carrier identification. Each volunteer, prior to having venipuncture performed, was asked to complete a 3 page questionnaire supplied by the California Tay-Sachs Prevention Program. Four factual questions, relating to the incidence of the carrier state and the probability of a carrier married to a noncarrier producing a child with Tay-Sachs disease, were all answered incorrectly by 73 per cent of the

tested population. We concluded that individuals participated in the screening programs due to a general concern for family welfare. Identified carriers, therfore, were "re-educated" during post screening counseling sessions. Counseling of carriers was accomplished quickly and individually by locally designated medical authorities. Efforts were made to discuss feelings and questions relating to the carrier state. These counseling sessions apparently sufficed to diminish anxiety and feelings of diminished self-worth. Although long-term studies are not yet available for confirmation, follow-up questionnaires were completed by carriers 3 months after counseling. The questionnaires indicated that carriers, who have a direct need to understand the facts, retained factual data relating to practical genetics and prenatal diagnosis. They also did not feel stigmatized. Carriers were eager to inform untested family members of this screening program. They did not appear to feel constrained in future marital choice or family planning. The carrier state was also freely acknowledged to friends.

Each community was asked to impose a voluntary testing fee of $8 per participant; however, no person was refused testing for inability or nondesire to pay. This fee was sufficient to pay for the cost of each individual's test performed by the California laboratory, plus all shipping, administrative, and intermediate laboratory costs. The total cost for all three communities was $4,640. Twenty-three carriers married to noncarriers and one couple in which both members were carriers were identified in this initial screening. The economic benefits to the identified couple and the relatives of the identified carriers cannot at the present time be calculated. As yet no pregnancies at risk have been monitored. It has been estimated that the cost of caring for one child with Tay-Sachs disease is approximately $40,000 during the few years of the child's life.[6] In the absence of this "prevented pregnancy" one can only conclude that at the present time the benefit of the program has been that the individuals screened were given an opportunity, at a reasonable cost to themselves, to diminish the chance of a fatal disease occurring within their immediate and nuclear family.

Comment

Understanding the limits of one's resources is the hallmark of a well-regionalized program. Large geographic areas and long distances between cities made mandatory the delegation of responsibility to local leaders. Community control of the program enhanced local pride and hopefully increased compliance. The community voluntarily screened itself. Community leaders felt secure having available, on a consultative basis, the skills and experience of the clinic staff.

The obstetrician-gynecologist plays an important role in continuing this program of preventive medicine. Nonpregnant Jewish women can have the blood test for carrier determination performed at many centers throughout the country. The American College of Obstetrics and Gynecology is currently preparing an "ACOG Technical Bulletin"* identifying physicians to whom patients and blood samples may be referred for screening. If a woman is a carrier, her husband's blood should be tested. If both husband and wife are identified as carriers, each pregnancy has a 25 per cent chance of producing a child with Tay-Sachs disease. The detection of the at-risk couple will allow prepregnancy counseling and referral for appropriate testing during pregnancy. This fatal childhood illness can be detected in the unborn child at 16 week's gestation, via amniocentesis followed by hexosaninidase A evaluation of the amniotic fluid and exfoliated cultured fibroblasts. If the couple is not seen until the woman is pregnant, the prospective father's serum should be sent for immediate analysis. If he is not a carrier, there is no chance that a child with Tay-Sachs disease will be born. If he is a carrier, the wife must then be tested. As pregnancy often causes false-positive serum results, a more specific white blood cell test must be performed on the wife's blood sample. If both prospective parents are carriers, genetic amniocentesis is indicated. If time is of the essence, the husband's and wife's tests can be performed simultaneously. Although Tay-Sachs disease is rare, the alert obstetrician can prevent his Jewish patients from suffering the tragedy of having a child with Tay-Sachs disease.

Regionalization can bring the latest medical advances to smaller cities in an economically and technically feasible way. This has been demonstrated by the regionalization of a Tay-Sachs screening project for middle Tennessee. The experience gained in this program will be used to help implement other birth defects prevention programs in this region. The obstetrician has a unique role as an advocate of and participant in preventive services. He can provide the expertise in identifying and counseling those high-risk individuals who might benefit from prenatal testing and counseling.

The authors would like to thank Dr. Michael Kaback, Ms. Susan Greenwald, and their staff at the California Tay-Sachs Disease Prevention Program for their invaluable help.

*No. 34, January, 1976.

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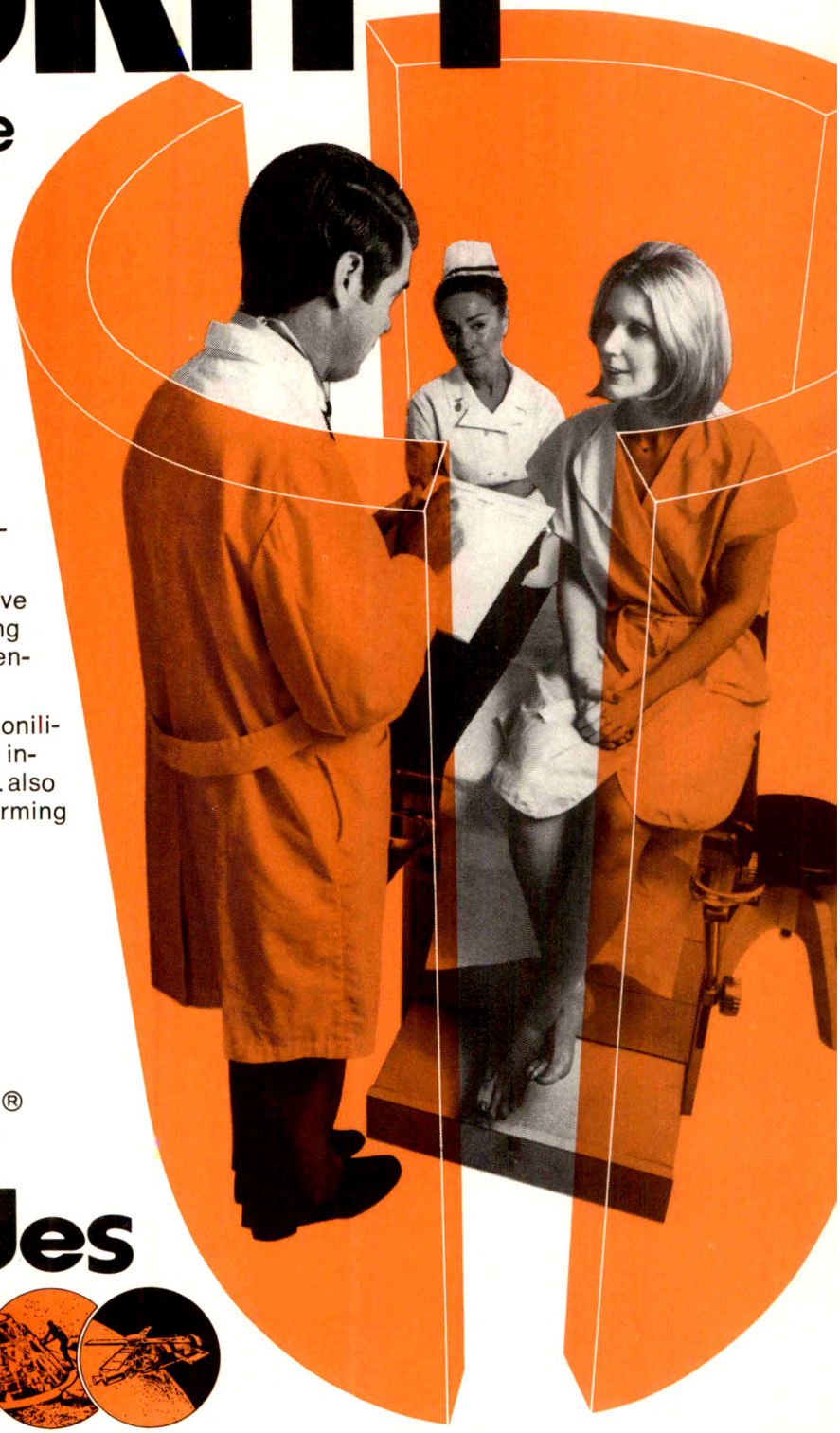
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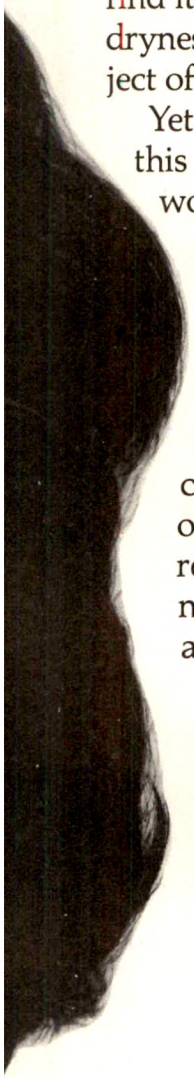


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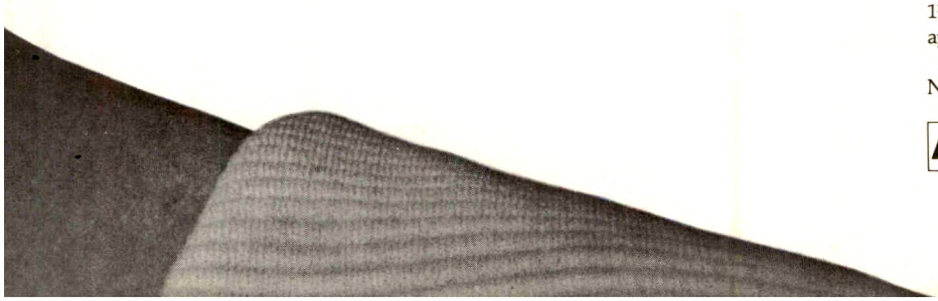
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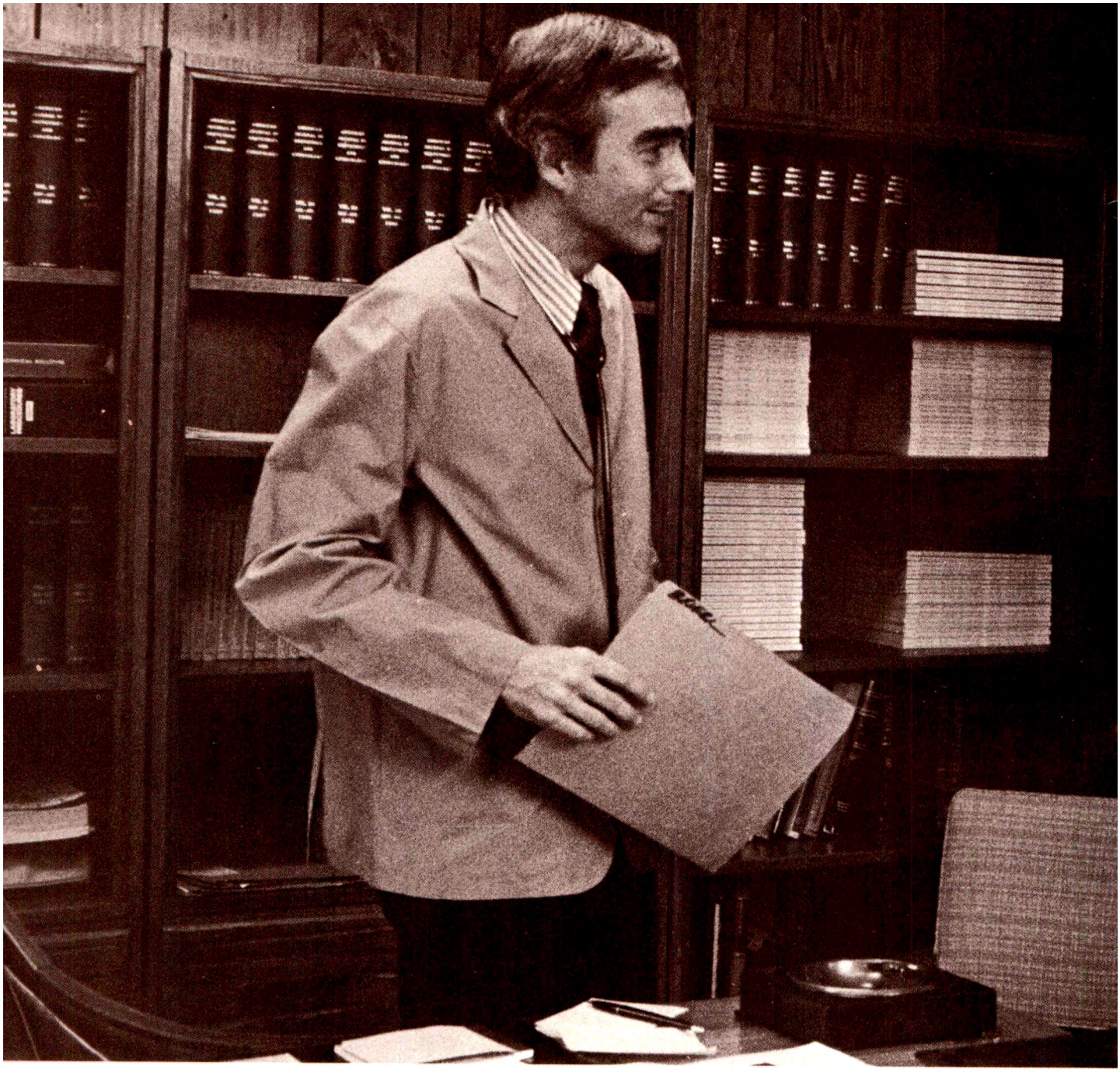
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Norlestrin achieves its contraceptive effect primarily by inhibition of ovulation through gonadotropin suppression. It is possible that other sites of action such as changes in cervical mucus and in the endometrium may contribute to the high efficacy of oral contraceptives.

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease, and reduced tolerance to carbohydrates, have not been quantitated with precision.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATION

Norlestrin is indicated for the control of conception.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.
6. Pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
3. Since the safety of Norlestrin (norethindrone acetate and ethinyl estradiol) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period.
4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.
2. Endocrine and possibly liver function tests may be affected by treatment with Norlestrin. Therefore, if such tests are abnormal in a patient taking Norlestrin, it is recommended that they be repeated after the drug has been withdrawn for two months.
3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size.
4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.
6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
7. Any possible influence of prolonged Norlestrin therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.
8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving Norlestrin therapy.
9. The age of the patient constitutes no absolute limiting factor, although treatment with Norlestrin may mask the onset of the climacteric.
10. The pathologist should be advised of Norlestrin therapy when relevant specimens are submitted.
11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Pulmonary embolism
Cerebral thrombosis

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea during and after treatment
Edema
Chloasma or melasma
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)
Changes in cervical erosion and cervical secretions
Suppression of lactation when given immediately postpartum
Cholestatic jaundice
Migraine
Rash (allergic)
Rise in blood pressure in susceptible individuals
Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post-treatment
Premenstrual-like syndrome
Changes in libido
Changes in appetite
Cystitis-like syndrome
Headache
Nervousness
Dizziness
Fatigue
Backache
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: increased sulfobromophthalein retention and other tests; Coagulation tests: increase in prothrombin Factors VII, VIII, IX, and X; Thyroid function: increase in PBI, and butanol-extractable protein-bound iodine and decrease in T^3 uptake values; Metyrapone test; Pregnanediol determination.

SPECIAL NOTE

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new compact on the fifth day (Day 5). Persistent bleeding which is not controlled by this method indicates the need for re-examination of the patient, at which time nonfunctional causes should be borne in mind.

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FETUS, PLACENTA, AND NEWBORN

Fetal alcohol syndrome: Seven new cases

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In one year, the "fetal alcohol syndrome" (FAS) was recognized in seven newborn and older infants, bringing the total in the current literature to 26 cases. This recently rediscovered disorder consists of severe prenatal and postnatal growth failure, mental deficiency, and characteristic hypoplasia of the middle face and orbits with minor malformations of the heart and joints. The mothers have chronic alcoholism. By identifying and counseling such women, obstetricians and gynecologists may prevent the occurrence of the syndrome or diagnose it in the neonate.

THE AFFECTED infants were ascertained in various medical settings of The Johns Hopkins University School of Medicine, most often for maternal neglect or failure to thrive; however, two newborn patients were diagnosed because alcoholism had been recognized in the mothers before delivery. The first patient, reported in detail, epitomizes the syndrome. Selected aspects of the other cases are noted briefly and clinical details are summarized together with previously reported cases[1–7] (Table I, Figs. 1 to 3).

Case reports

Patient 1. The mother's five prior pregnancies by different men produced, in sequence: two term infants (normal on examination at ages 14 and 13 years), one premature infant, unavailable for examination, and two miscarriages of unknown gestational age. Beginning after her first two pregnancies, the mother's alcoholism with wine and beer was recognized for at least 10 years by physicians, social workers, family, and herself. Her disease was complicated by mild pancreatitis and slight abnormalities of liver function. During the last 5 months of a 37 weeks' pregnancy, she was given vitamins and regular prenatal care and, 4 weeks before delivery, had one episode of abdominal pain, called alcoholic gastritis. After normal labor and delivery, the infant developed hyperbilirubinemia, which peaked at 15 mg. per 100 ml. and subsided after 24 hours of phototherapy. Irritability and tremulousness, first noted on the third day, were not explained by sepsis or abnormalities of serum glucose, calcium, or phosphorus, and persisted to discharge on day 21.

At age 23 months (Fig. 2, *A* and *B*), weight was 8,160 grams, length 78 cm., and head circumference 45.5 cm. (fiftieth Stuart percentiles for 7, 15, and 9 months, respectively). He had occipital flattening and balding, right ocular ptosis, a high-pitched cry, left cryptorchism (inguinal testis), lack of complete extension of both knees, right transitional simian crease, and a small café-au-lait spot on the left buttock. The left palpebral fissure was 18 mm. long, the right 20 mm. The palate, pinnae, and heart were normal. Other neurologic tests were normal except for mental development: the

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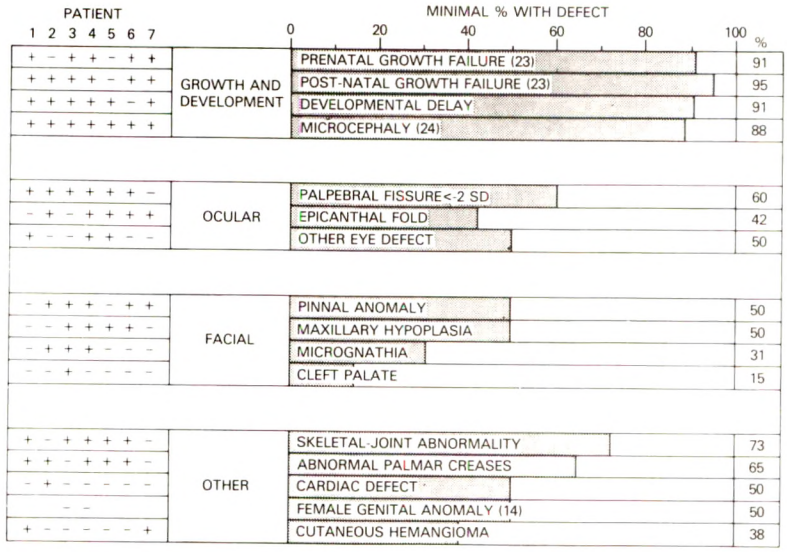


Fig. 1. Minimal frequency of defects in 19 published cases[1–7] and the present seven patients. In parenthesis is the number of informative cases, if not 26. Key: +(present), −(absent).

Table I. Characteristics of mother, gestation, and birth

Characteristic	*Patient (race and sex)**							
	1 BM	*2* BM	*3* BF	*4* MuF	*5* BM	*6* BM	*7* BM	*Mean (No.†)*
Age of onset of alcohol abuse (yr.)	22	22	25	21	23‡	23‡	27	22.4 (18)
Duration of abuse (yr.)	10	8	6	10	2	6	3	7.3 (20)
Maternal age at delivery (yr.)	32	30	31	31	25	29	30	30.3 (23)
Birth order	6/6	9/9	7/7	4/4	5/6	6/6	5/5	5.3/5.6 (22)
Weight gain during pregnancy (Kg.)	10	6	5	—	—	7	43	4.0 (15)
Duration of pregnancy (wk.)	37	28	34	40	34	40	—	37.3 (23)
Weight at birth (Kg.)	1.95	1.17	1.38	1.59	2.69	2.47	2.95	1.84 (26)
Length at birth (cm.)	44	37	37	40.5	48.5	—	—	42.3 (21)
Head circumference at birth (cm.)	30½	28	28	—	34	—	—	30.1 (19)
Apgar score at one minute	9	6	1	5	§	—	§	6.2 (18)
Age at diagnosis (mo.)	23	1	0	14	50	13	10	19 (26)

*Abbreviations: B, black; Mu, mulatto; M, male; F, female; —, unknown.
†Number with information (26 infants born in 25 gestations to 23 different mothers).[1–7]
‡Same mother.
§Delivered at home.

Bayley test indicated a mental age of 13 months and a motor age of 14 months; the Vineland social maturity quotient was 51.

Laboratory examinations, many carried out before age 4 months, included negative or normal values for routine serum chemistries, protein, IgM, urinalyses, VDRL, electroencephalogram, karyotype, intravenous pyelogram, and assay for abnormal amino acids or other metabolites in urine. By 23 months of age, skull radiographs, normal at age 2 months, showed no digital markings, a thickened calvarium, and schlerotic sutures, suggesting poor brain growth. Skeletal radiographs showed small orbits and delayed mineralization of terminal phalanges of fourth and fifth toes. Bone age was consistent with chronologic age.

Patient 2. Results of the mother's prior pregnancies included two abortions and a premature birth. Alcoholism with gin and beer, also present in her husband and siblings, was complicated by liver disease and delirium tremens. When she presented for pre-

natal care in mid-trimester, she was treated for gonorrhea and positive serology for syphilis. At 28 weeks of gestation, while recovering from emergency laparotomy which revealed hemorrhagic (alcoholic) gastritis, she precipitously delivered without sterile precautions. The baby had respiratory distress and received antibiotics for presumed neonatal sepsis. Fluorescent treponemal antibody was present in cord blood at a titer of 1:60, with IgM-specific antibody of 1:10. Cerebral spinal fluid serology was repeatedly negative and blood serology was negative at age 5 months. At age 15 months (Fig. 2, *C*), dysmorphic features beyond those in Fig. 1 included low-set ears with prominent antihelix, a 6 by 6 cm. anterior fontanelle, and a Grade 2/6 systolic murmur, considered to be pulmonary artery stenosis. Psychomotor development was delayed.

Patient 3. The pregnancy was complicated by maternal anemia (hematocrit 25 per cent), consistent with a toxic anemia of alcoholism on bone marrow examination. When the mother presented in labor, she appeared to be acutely intoxicated from alcohol. She had postaxial polydactyly of the hands and a history of partial pneumonectomy for tuberculosis 4 years before the birth of the patient. Her prior pregnancies by different men resulted in three term infants, one early abortus, and two premature infants (one stillborn, one with club feet). The patient's dysmorphic features included low-set ears, bilateral sixth fingers, cleft soft palate, and bilateral talipes equinovarus. At 5 months of age, her Denver Developmental Evaluation was at 4 weeks' level.

Patient 4. Throughout pregnancy, the mother daily consumed six cans of beer and a quarter of a liter of Scotch, smoked heavily, ate poorly, and, in the first trimester, took decongestants and aspirin for a chronic cold. Besides a spontaneous abortion, prior pregnancies by different men resulted in a term infant weighing 1.9 kilograms and a 7 month premature infant, both said to be normal at ages 7 and 4 years. During these gestations, alcohol was allegedly not used to excess. Patient 4 (Fig. 2, *D*) spent her first month in a premature nursery because of low birth weight and was hospitalized with bronchiolitis at age 4 months. Skeletal defects included a large anterior fontanelle, bilateral talipes calcaneovalgus and, in the hands, polydactyly and hyperplasia of the second and fifth middle phalanges. At age 20 months, Bayley testing showed a mental age of 16 months and a motor age of 15, and the Vineland social quotient was 103.

Patients 5 and 6. When first evaluated at age 6 months, Patient 5 was thought to have delayed development with normal growth, because of presumed hypoxia during birth at home. IQ was 41 by Cattell Infant Intelligence Scale and the Vineland social quotient was 41. When FAS was diagnosed in his younger brother, Patient 5 was re-examined at age 50 months, and the syndrome was recognized because of bilateral esotropia, decreased supination bilaterally, and short palpebral fissures. Bilateral cervical ribs and persistent rhinorrhea were also noted. After delivery of Patient 6, the mother shot the father and, 3 weeks later, was found dead in her apartment. Autopsy revealed fatty metamorphosis of the liver, atrophic gastritis, and mild glomerulonephritis and pyelonephritis. Patient 6 had mild neonatal respiratory distress, clinodactyly, sacral dimple, and diminished elbow extension and supination accompanying severely delayed growth and development.

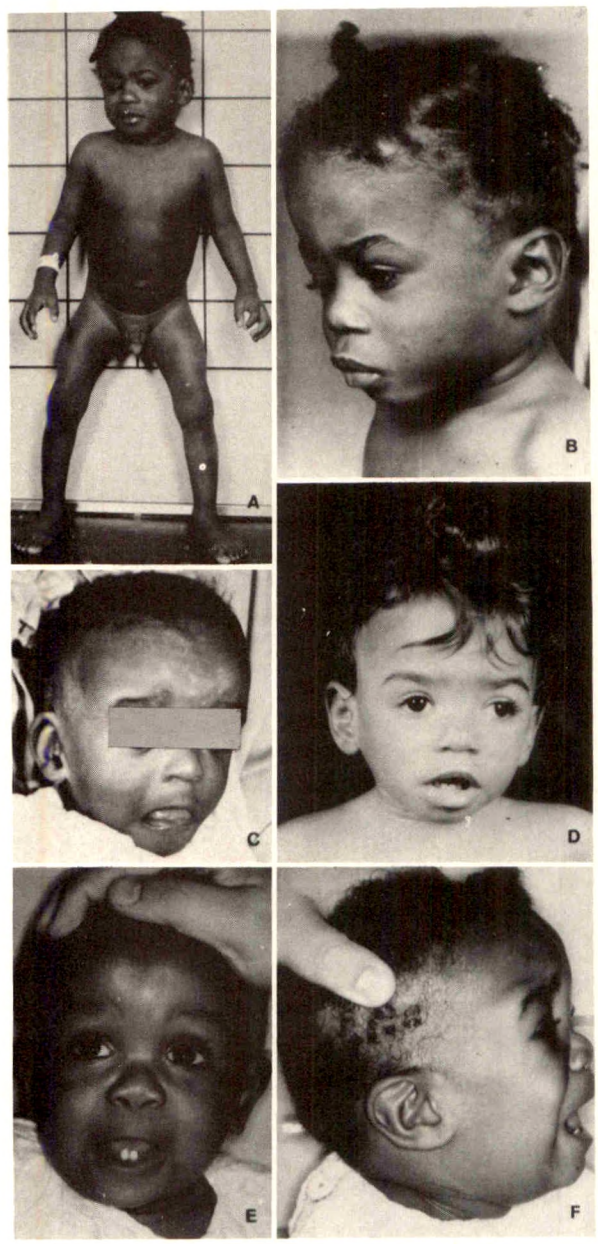


Fig. 2. Patients 1 (*A* and *B*), 2 (*C*), 4 (*D*), and 7 (*E* and *F*).

Patient 7. By age four months, this boy (Fig. 2, *E* and *F*) was hospitalized three times because of neglect, with

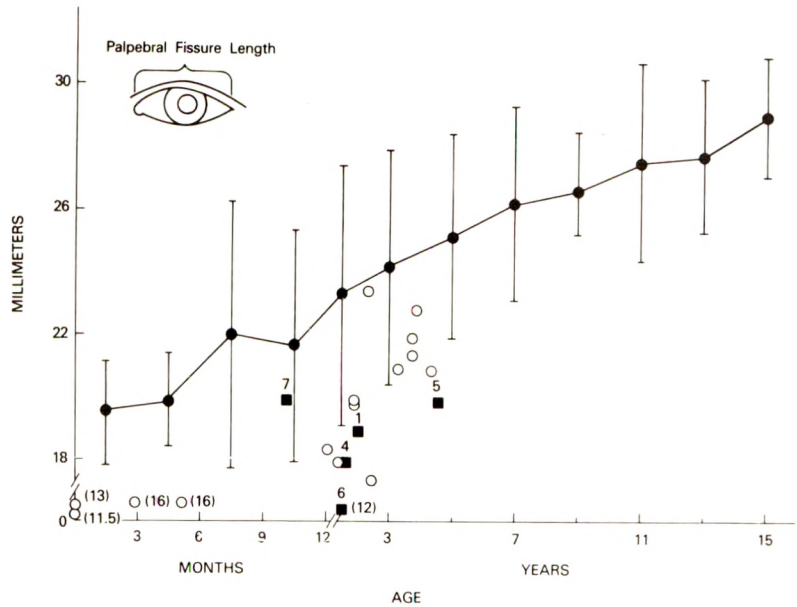


Fig. 3. Growth in length of palpebral fissure (measured as shown in insert). Means ± 2 S.D. were calculated from data for white children.[8] Squares indicate present cases with patient number on top; open dots are all published cases in which information was available. Number in parentheses beside symbol is actual measurement, if less than 17.5 mm., the break in the ordinate.

the mother often drunk. Remarkable features were a 2 by 2 cm. cutaneous hemangioma of the left forearm and signs of neurologic impairment at age 6 months (tremulousness, occasional cortical thumbs, and slight rigidity of upper limbs). Four older half-siblings, born before severe maternal alcoholism, were said to be normal.

Comment

The present series confirms and extends findings in recently published cases[1–7] and makes a total of 14 females and 12 males in three races (whites, blacks, and American Indians). The patients may first present to a variety of health professionals, including the obstetrician alert to the sometimes subtle manifestations of chronic alcoholism. The mothers are multiparous, with long-standing, severe alcoholism from all types of beverages—wine, beer, and spirits. Despite variations in estimated duration of pregnancy (12 premature, nine term, and two prolonged), birth measurements fall below average for gestational age. The babies are small for dates in an unusual way, with birth length more severely decreased than birth weight and head circumference. In maternal malnutrition, the opposite holds: fetal weight is more retarded than length.[9] During infancy, however, the FAS patients increase more in length than in weight, while remaining small.

Analysis of dysmorphic features in 26 cases (Fig. 1) indicates that no defect is pathognomonic, but ocular and facial anomalies predominate. Prior reports emphasized a high frequency of short palpebral fissures, although there are three *caveats:* (1) palpebral fissures are difficult to measure; (2) normal standards are from an old survey of 243 white children[8]; (3) when S.D.'s are calculated from the original data, eight cases of FAS are within two deviations from the mean, although all are below average (Fig. 3). Nonetheless, objective measurement remains important, since primary hypoplasia of the entire globe and orbit in FAS may give the impression of normal palpebral fissures. Other common eye abnormalities include epicanthal folds (11 patients), convergence defects (five), and ptosis (five).

In most cases, skeletal defects are mild, such as camptodactyly, clinodactyly, and decreased range of motion at elbow, hip, or knee, but several patients had hip dislocation. The joint problem and frequently abnormal palmar creases may reflect neuromuscular dysfunction in utero since normal joint and crease development depends on adequate joint motion during morphogenesis. Cardiac defects are likewise frequent but mild. Of 13 patients with suspected congenital heart disease, four were considered to have ventricular septal defects that spontaneously closed and only two required surgery or cardiac catheterization.

Mental deficiency is common and may be the most sensitive manifestation of maternal alcohol abuse during pregnancy. For example, Patient 5 would have remained undiagnosed had not the full FAS been

obvious in a subsequent sib, more heavily exposed to alcohol in utero.

Some may doubt the validity of the syndrome. It is not new, but has been rediscovered several times, as suggested by reports from France[10] and previously cited historical references.[2] The FAS can be readily distinguished from other patterns of multiple malformations which share some features, such as the syndromes of Cornelia de Lange, Smith-Lemli-Opitz, trisomy-18, familial blepharophimosis,[11] and fetal hydantoin.[12] The diagnosis is based on a typical maternal and gestational history with signs of prenatal and postnatal growth deficiency, delayed development, short palpebral fissures, and cardiac or joint anomalies which may be minor; these features are, admittedly, nonspecific and quite common.

But the syndrome also may be frequent, like alcoholism. Among the offspring of 23 clearly alcoholic women in the Collaborative Perinatal Project, six cases of FAS (26 per cent) were found, as judged by minimal data in the clinical records (vs. none in controls).[13] Of 76 sibs and half-sibs of 21 probands in the literature, seven (9 per cent) have the syndrome. This must be a low estimate, since some of the pregnancies antedated maternal alcoholism. The occurrence of FAS is likely to reflect the amount and duration of fetal exposure to alcohol; however, it is plausible that genetic polymorphism of enzymes for ethanol metabolism may alter fetal susceptibility,[14] as suggested by a mouse model of the FAS.[15] In fact, ethanol may not be the only teratogen in alcoholic beverages. The primary teratologic action may be potentiated by other compounds that cross the placenta, such as aldehydes and heavy metals,[16] and by the social and medical complications of alcoholism, such as inadequate nutrition, altered intermediary metabolism, and irregular medical care.

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Placental lesions in experimental toxemia in the rabbit

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Unlike the normal human placenta, the normal rabbit placenta, near term, is essentially free of such stigmas of aging as infarcts and syncytial knots. When experimental toxemia is produced in the pregnant rabbit by ligating the terminal aorta to a specific degree of stricture, placental lesions resembling those found in human toxemia are observed; namely, diffuse congestion, old and recent infarcts, and syncytial knots. All the treated animals who exhibited anatomical and clinical signs of toxemia presented, in association, obvious placental lesions; there were, however, some animals which showed infarcts but no other signs of toxemia.

A PREVIOUS communication[1] described a method for producing experimental toxemia in the pregnant rabbit by ligating the terminal aorta to a specific range of stricture. Rabbits so treated in the latter half of gestation developed hypertension, proteinuria, and fluid retention. Renal lesions were demonstrated using light microscopy, electron microscopy, and immunofluorescence; focal liver necrosis was also found. Many rabbits developed intrauterine fetal death and their placentas were often grossly hemorrhagic. The purpose of this communication is to describe the placental lesion in some detail.

Although several investigators have produced toxemia of pregnancy by creating ischemia to the uteroplacental unit,[2–10] only two have recorded information about the placenta and even that in no detail. Berger and Cavanagh[7] described and illustrated gross ischemia in that part of the placenta where the blood supply was reduced by a Z suture. Douglas and Langford[8] observed separation and necrosis of the placenta, having produced ischemia by wrapping the uterus in cellophane. In addition, Symeonidis,[11] who injected pregnant rats with progesterone, described congestion and periplacental hemorrhage accompanied by disappearance of the Langhans layer and degeneration, atrophy, and necrosis of syncytiotrophoblast.

By contrast with animal studies, there is an extensive literature dealing with lesions in the human placenta associated with pregnancy toxemia and its severest form, eclampsia. The monograph of Sheehan and Lynch[12] on the pathology of toxemia of pregnancy restricts itself to lesions found in the mother at autopsy and does not include a study of placental lesions. The monograph on the human placenta by Benirschke and Driscoll[13] deals with the placenta in toxemia as part of the general question of circulatory disturbances, especially as manifested by infarction. But the special pathology of the placenta in toxemia of pregnancy has been studied by many observers.

Notable among these are the observations by Tenney and Parker,[14, 15] who described increased aging and degeneration of syncytiotrophoblast in the toxemic placenta and concluded that placental histology was an accurate gauge of toxemia of pregnancy. Bartholomew and associates[16–18] emphasized the importance of placental infarcts as the visible sign of toxemia and developed criteria by which toxemia could be diagnosed from unknown specimens. Wigglesworth[19] noted persistence or reappearance of cytotrophoblast in toxemia placentas, and McKay and associates[20] and Wislocki and Dempsey[21, 22] showed that this was due to active regeneration. Other observers have noted lesions

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Table I. Placental lesions in rabbits

	Normal (5)	*Mild toxemia (4)*	*Severe toxemia (11)*
Congestion of villi	None	Diffuse	Massive
Fresh infarcts	None	Small, rare	Large, multiple, confluent
Older infarcts	None	Rare	Occasional
Early syncytial degeneration (swollen nuclei)	None	Occasional	Very frequent
Late syncytial degeneration (pyknotic nuclei)	Rare	Frequent	Very frequent
Decidual hematoma	None	Slight	Frequent
Fibrin deposition	None	Diffuse	Diffuse

in decidual arterioles which simulate those seen in hypertensive states, and Tominaga and Page[23] concluded that the diverse anatomic changes seen in the toxemic placenta could be explained as an accommodation to hypoxia, i.e., reduced perfusion. Salvatore[24] explained the inconstancy of placental lesions by their dependence on the duration and severity of the disease, and Maqueo and associates[25] found that acute infarcts were present five to 15 times more often in toxemic placentas and that the frequency of infarction was related to the severity of the disease.

It should be stated at the outset that there is no placental lesion that is pathognomonic for toxemia, nor does the finding of a constellation of lesions associated with toxemia make the diagnosis more certain. Any and all of the morphologic changes described in the human toxemia placenta can be found in nontoxemic subjects as the result of other conditions. When a pathologist sees a placenta with infarcts, syncytiotrophoblastic degeneration, cytotrophoblastic regeneration, pronounced deposition of intervillous fibrin, endarteritis, or hyalinization of decidual arterioles, he can only inquire whether the clinical setting justifies his suspicions.

Material and methods

Fifteen placentas were selected from the rabbits rendered toxemic by ligating the terminal aorta during the last half of pregnancy. Excluded from the study were those placentas associated with premature separation, those associated with intrauterine fetal death and maceration, and those which delivered spontaneously but which were not fixed in formalin immediately. The excluded placentas were those in which natural autolysis or delayed fixation might produce artifacts. In addition, five placentas were selected from untreated rabbits as controls. In all, 20 placentas were studied, and their repartition follows: (1) eleven placentas from rabbits at term with manifest signs of experimental toxemia, i.e., the full syndrome; (2) two placentas from rabbits with manifest signs of experimental toxemia killed 8 days before term (pregnancy in the rabbit lasts 28 to 32 days); (3) two placentas from rabbits that developed isolated signs of experimental toxemia; (4) five placentas from normal rabbits at term without aortic constriction, used as controls.



Fig. 1. Low-power view of the placenta from an untreated control showing a thin layer of amnion (right) and uniform cords of trophoblast arranged in lobules. There is no congestion, ischemic change or infarction.

The term placenta of the rabbit is a discoid organ 2 to 3 cm. in diameter and 3 to 5 mm. in thickness. Three or four representative slices were taken through the full thickness of each placenta used for study and immediately fixed in neutral buffered formalin. They were stained with hematoxylin and eosin by standard methods. No special stains were used. Gross weights and measurements were not recorded, but the placentas from toxemic rabbits were obviously mottled, with reddish-purple zones of hemorrhage when inspected on both fetal and maternal surfaces.

The principal object of this study was to present the microscopical changes.

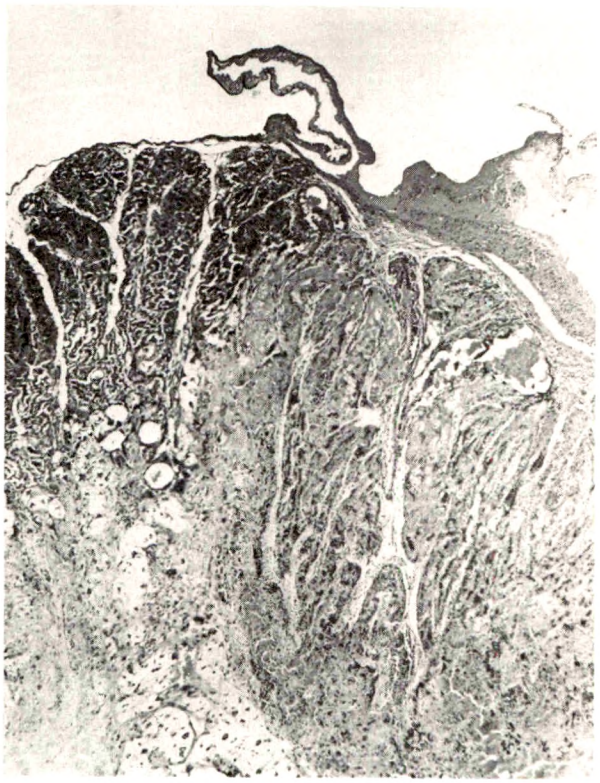


Fig. 2. Low-power view of the placenta from a rabbit with severe toxemia showing hemorrhagic infarction of the subamniotic aspect of a lobule (left) contrasted with well-preserved trophoblastic columns (right). Degenerative vacuolation is seen in the zone beneath the infarcted trophoblast where it fuses with symplastic endometrium.



Fig. 3. Medium-power view of placenta from a rabbit with severe toxemia showing diffuse congestion of vessels between trophoblastic lamina and hemorrhagic infarction of the cords.

Observations

Because the number of specimens in Groups 2 and 3 is small, we have combined them into one group, thereby giving a distribution of five normal placentas as untreated controls, four with mild toxemia, and 11 with severe toxemia. The observations are summarized in Table I.

The placentas from untreated rabbits showed the usual configuration of long columns of trophoblast usually seen as a double layer surrounding a central vessel. The columns extended from the amniotic surface to the decidual plate where they fused with the symplastic endometrial glandular epithelium. These placentas were free of congestion, infarction, syncytiotrophoblastic knots, and intervillous fibrin (Fig. 1). At the junctional zone between trophoblast and decidua, cells were normally vacuolated, and the cell margins of decidual cells were blurred.

The placentas from rabbits with mild toxemia showed diffuse congestion of the thin-walled capillaries between trophoblastic columns. The columns were thickened thereby and the intervillous space narrowed. Focal necrosis with petechial hemorrhage was seen in the decidua, and delicate strands of fibrin were deposited both near these foci and on the free margin of the placenta. Focal calcification of minor degree was noted in one specimen. No large deposits of intervillous fibrin were found nor was there any infarction of the trophoblastic columns or degenerative change in the syncytiotrophoblast. One specimen in this group showed a small thrombus in a decidual vein, but no major thromboses were evident.

The placentas from the 11 rabbits with severe toxemia showed extensive changes. The most prominent lesion was acute hemorrhagic infarction of trophoblastic columns, often extending from the fetal surface through the entire thickness of the trophoblastic zone, commonly involving a major segment of a placental lobe (Figs. 2 and 3). Also present were a few areas of older infarction, evidenced by less of hemoglobin pigment from red blood cells, traces of hemosiderin, and loss of nuclear staining of trophoblast (Fig. 4). Lines of demarcation between infarcted and preserved tissue were usually distinct, but occasionally a pale zone of ischemia with pyknotic cells bordered the area overrun by hemorrhage (Fig. 5). An earlier stage was



Fig. 4. Low-power view of the placenta from a rabbit with severe toxemia showing acute hemorrhagic infarction of the margin of a lobule (center), spared trophoblast (left), and nonhemorrhagic infarction (coagulation necrosis of the adjacent lobular margin (right).



Fig. 5. A thin layer of pyknotic cells and vacuolated cells separates the zone of hemorrhagic infarction from the zone of endometrial attachment.

detected in some sections where multiple small discrete foci of ischemic necrosis were found in individual lobes (Figs. 6 and 7). The inference is made that as such small foci enlarged and coaslesced they became hemorrhagic.

Degenerative changes in syncytiotrophoblast were seen with frequency in noninfarcted placental tissue, swollen cells representing an early stage and pyknotic nuclei forming knots representing a later stage (Figs. 8 and 9). Large areas of hemorrhage, equivalent to retroplacental hematoma, were seen in the decidua. Thrombosis of decidual veins near such hemorrhage was common, and a few decidual arterioles showed atheromatous changes in their intima. Abundant fibrin was deposited not only between trophoblastic cords but at the perimeter of zones of infarction and to a lesser degree even in the uninvolved placental tissue as well.

Comment

The human placenta, like the rabbit placenta, is hemochorial, but the latter does not have mesodermal

organ secreting only small amounts of chorionic gonadotropin and showing even in normal pregnancy focal calcification, reduction in the caliber of villi, coarsening of collagen in villous stroma, areas of intervillous fibrin deposition which may be large, formation of syncytial knots, and even old infarcts. By contrast, at term the rabbit placenta is free from these stigmas of aging, showing at most a few syncytiotrophoblastic knots and perhaps a minute focus of infarction in isolated trophoblastic columns. Infarction, old or recent, is the cardinal sign of toxemic change in the placenta, but in the human being it is a quantitative distinction, inasmuch as infarcts are seen in nontoxemic placentas, often occupying a considerable portion of its substance. Benirschke and Driscoll[13] emphasized that compromised maternal circulation is the usual cause of placental infarction in the human subject, especially in toxemia of pregnancy.

Observations in this study indicate that in the rabbit, as in the human subject, infarction and the changes associated with it are the principal signs of toxemia. But



Fig. 6. Low-power view of a placental lobule in a rabbit with mild toxemia showing multiple foci of bland ischemic necrosis of trophoblast (arrows).



Fig. 7. High-power view of one of the ischemic foci in Fig. 6.

toxemia did exhibit fresh and old placental infarcts, but a few rabbits in which uteroplacental ischemia had been created by ligating the terminal aorta did not survive long enough to develop the clinical signs of toxemia, viz., hypertension, albuminuria, and fluid retention. Yet they did exhibit placental infarction of a lesser degree. This observation on the small number of rabbits in the "mild toxemia" group leads us to speculate that the initial event in toxemia of pregnancy is reduction of blood flow to the uteroplacental unit resulting in placental ischemia, often to the point of infarction, and that the systemic effects in the mother are secondary. Perhaps this reasoning explains why Bartholomew and associates[17] had a 20 per cent false-positive error in diagnosing toxemia of pregnancy from examining the placentas from pregnancies whose clinical features were unknown to them. They had no false-negative errors, and perhaps the infarcts in the false-positive cases were an index of "latent" or "occult" toxemia which might have become clinically manifest had the pregnancy continued longer. If so, we can offer a maxim couched in negative terms: no toxemia without infarction—even though the converse need not be absolutely true. In the rabbit, the presence of hemorrhagic infarction is almost a qualitative point of distinction between the normal and the toxemic placenta.

Diffuse congestion of the trophoblastic cords was a prominent feature in the placentas of both mild and severe toxemia in this set of observations, and it is not unreasonable to conceive of congestion as preceding infarction. The mechanical effect of congestion of trophoblastic cords is to narrow the intervillous space, and its hemodynamic effect is to reduce blood flow from the maternal inflow openings, thereby accentuating the ischemia produced by aortic stricture.

Open for further exploration is the question of what biochemical alterations occur in the uterus and placenta as the result of ischemia and whether specific substances are released into the uterine venous drainage and produce the clinical signs and pathological lesions of toxemia of pregnancy. Nor ought it be overlooked that placental ischemia may alter the permeability of the amniotic membrane and substances in the amniotic fluid may be equally as responsible as those from the chorion for selected aspects of the disease.

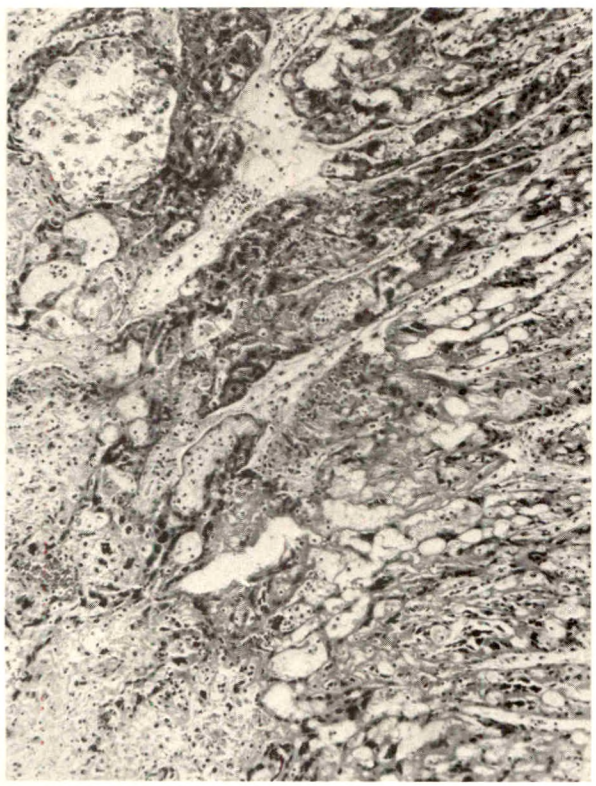


Fig. 8. Cytoplasmic swelling and vacuolation in a severely ischemic placenta at the junction between trophoblastic cords and endometrium.



Fig. 9. An island of placental tissue in an otherwise well-preserved segment showing dilated sinusoids, condensation of cytoplasm, and nuclear pyknosis with early knot formation.

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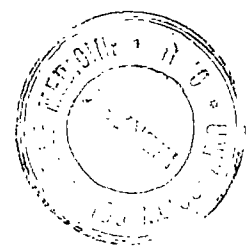
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Thyroid function in human pregnancy

IX. Development or retardation of 7-year-old progeny of hypothyroxinemic women

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Progeny of women, whose thyroid function was studied gestationally, had psychological and/or neurologic examinations at 8 months, 4 years and 7 years of age. In more than 100 pregnancies (at least 3 per cent of total pregnancies) hypothyroxinemia occurred and was treated adequately or inadequately. Children were delivered after uncomplicated pregnancies (except hypothyroxinemia), had birth weights of at least 2,500 grams, and were excluded when postnatal insults intervened. At 8 months and 4 years progeny of inadequately treated hypothyroxinemic women had the lowest psychological scores. Now 246 7-year-old children have been examined psychologically and neurologically (earlier data on only 101). Definite trends and a few statistically lower psychological scores of progeny of inadequately treated hypothyroxinemic pregnant women are compared with better psychological scores of 7-year-old children born to euthyroid and adequately treated hypothyroxinemic women. In six sibling sets outcome was better when hypothyroxinemic women were treated with adequate thyroid replacement therapy. If a woman has a poor reproductive history, early in a subsequent gestation, thyroid status should be examined and adequate thyroid medication considered seriously.



THE RELATIONSHIP between thyroid function of the pregnant woman, the fetus, and the infant still remains a challenge in human development or lifetime retardation. Complexities of the problems are exemplified by titles and the subject matter of Three Symposia at the Kroc Foundation for the Advancement of Medical Science: 1972, *Human development and the thyroid gland; relation to endemic cretinism*[1]; 1973, *Endocrine aspects of malnutrition; Marasmus, kwashiorkor and psychosocial deprivation*[2]; 1974, *Perinatal thyroid physiology and disease.*[3] Stanbury in the 1972 preface wrote, "The discussion then turned to the hearing problems in endemic cretinism, with consideration of its embryological, pathological and experimental aspects. This lead naturally into a consideration of thyroid hormone in the development of the central nervous system, and the interactions between the thyroid and environmental factors, such as nutrition, in central nervous system maturation."[1] In 1973 Parra and associates had used a battery of tests to investigate thyroid function in children with marasmus or kwashiorkor. They summarized that abnormal thyroid tests in extreme malnutrition reflected adaptive changes relative to the stage of caloric deprivation.[2] The 1974 Symposium included data on the rapid, accelerated changes in thyroidal metabolic housekeeping of neonates and

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Some of the data were presented in part, November 11, 1974, at a Symposium of the Kroc Foundation for the Advancement of Science, Santa Ynez, California.

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infants and suggested many investigative fields.[3] A fine discussion of "true mild hypothyroidism" or "mild hypothyroidism due to decreased thyroid reserve" has been presented by Ingbar and Woeber.[4] The older terms of "metabolic insufficiency" and "tired housewife syndrome" were dismissed; but "decreased thyroid reserve" was recognized by Ingbar and Woeber[4] and by Fisher.[5] An intimate relationship between thyroid metabolism and pregnancy and development of a retarded or normally developing child has been reviewed exquisitely by Burrow and Ferris.[6]

Data presented here were initiated from a study on the effect of maternal age on development of progeny. Children of women younger or older than the usual child-bearing age have long been considered inferior in development. Robert E. Cooke, M.D., questioned whether thyroid function of pregnant women under 18 or over 35 years of age would differ from thyroid function of women in the usual child-bearing age bracket of 18 to 35 years. Therefore, from 1962 to 1967 thyroid function of pregnant women was studied at Providence Lying-In Hospital; progeny of these women were examined psychologically and/or neurologically at ages 8 months, 4 years, and 7 years,[7, 8] Diverse phases of our study can be summarized by examination of titles of the eight papers previously published in THIS JOURNAL.[8 (I–VIII)]

A totally unexpected finding was that at least 100 or approximately 3 per cent of the women at the prenatal clinic, in otherwise uncomplicated pregnancies, were hypothyroxinemic (had lower serum BEI [butanol-extractable iodine values][7, 8 (V, VI), 9] but gestationally normally elevated TBG [thyroxine-binding globulin][8 (III)] than control euthyroid pregnant women). For various reasons some of the hypothyroxinemic women were given adequate and some inadequate thyroid replacement therapy. The children were observed to learn whether inadequate thyroid replacement therapy of hypothyroxinemic women might be one cause of mental retardation of progeny.[8 (V, VII, VIII)]

The incidence of hypothyroxinemic women in 100 pregnancies was significantly higher than the incidence of hyperthyroxinemic or hyperthyroid women in only 13 pregnancies. However, clinical articles on treatment of gestational hyperthyroidism exceed published reports on therapy for or outcome of gestational hypothyroxinemia. In our original count of 1,589 pregnancies at Providence Lying-In Hospital (1962-1967)[8 (V)] 48 pregnancies were classified "high BEI and/or hyperthyroidism and/or thyroid dysfunction: nodules or carcinoma of thyroid." In only 13 pregnancies of that group was the woman classified hyperthyroid with definite diagnosis and/or at least two elevated serum BEI. The other 35 pregnancies with "thyroid dysfunction" included: 22 women who registered late or clinical evaluation and serum BEI values were consistent neither with euthyroidism nor definite hyperthyroidism; three women with complications not directly related to the thyroid; and 10 women with thyroid problems; previous thyroidectomies, cancer of the thyroid, and postpartum removal of a multiple colloid adematous goiter. Of the 13 women classified above as hyperthyroid, one delivered a macerated fetus crown-rump aged 13 weeks, one delivered a stillborn 2,070 gram infant, two delivered premature infants—a boy 2,155 grams, and a boy 1,956 grams, who expired from pneumonia at 3 months of age. Only nine hyperthyroid women delivered neonates of 2,500 grams. Psychological examinations were obtained for four of the nine offspring. This small number prevents comparison of development of offspring of hyperthyroid and hypothyroxinemic women.

Subjects and methods

Informed consent was given by all women for their studies and observations of their progeny. In fact, the lack of thyroid tests on blood of progeny was because no mothers were asked that blood samples be obtained from their children. A few mothers requested that their children be examined for thyroid function, or that they, themselves, be followed after their pregnancies.

Clinical, prenatal examinations of the gravidas were conducted at the Providence Lying-In Hospital from 1962 to 1967; psychological and pediatric-neurologic examinations were evaluated at the Brown University Child Development Study according to protocols for 8 month, 4 year, and 7 year examinations specified by the Collaborative Perinatal Project of the National Institute of Neurological Diseases and Stroke.[10–12]

For progeny in this report all pregnant women had clinical evaluations of thyroid function with biochemical tests of serum BEI[8 (I, II)] and for the majority of patients TBG and TBPA (thyroxine-binding prealbumin) capacities.[8 (III, V, VI)] BEI concentrations of individuals who had had no recent radiopaque x-ray examinations were identical with T4-iodine values determined by Benotti's modification of the Murphy-Patee displacement technique. In 13 sera the mean of calculated T4-iodines by Benotti's technique[13] was 4.5 and the mean BEI 4.4 μg per 100 ml. Since the present displacement or competitive binding techniques and radioimmunoassays usually report T4 (thyroxine) our normal range for gestational serum BEI has been calculated as T4 (Table I). The BEI is multiplied by 100/65.3 because iodine is 65.3 per cent of the

Table I. Normal range of serial serum T4 $\left(BEI \times \frac{100}{65.3}\right)$ 12 to 16 weeks to term in 356 uncomplicated, euthyroid pregnancies—living infant of 2,500 grams or more*

Mother's Age (yr)	*No. of pregnancies*	*T4 No.*	*T4 $\left(BEI \times \frac{100}{65.3}\right)$† (μg/100 ml.)*
14-17	94	264	9.2 –14.5‡
18-34	210	1,202	8.4 –14.5‡
35-44	52	252	8.4§–14.5
	356	1,718	

*From Fisher, D. A., and Burrow, B. N., editors: Perinatal Thyroid Physiology and Disease (Kroc Foundation Series, vol. 3), New York, 1975, Raven Press, p. 118.

†Serum T4 of 88 women aged 18 to 44, and 6 weeks or more postpartum, 4.9 to 9.8 μg/100 ml.

‡Sporadic 16.1 not abnormal.

§Sporadic 7.6 not abnormal for grand multiparae > 35 years.

thyroxine weight. No esoteric corrections were made for T3 (triiodothyronine) or free T4 in that formula. The requirements for women to be classified euthyroid were two normally elevated gestational BEI before and two after 24 gestational weeks.[8 (I, II)] The hypothyroxinemic women were so classified after two low BEI or one low BEI and an additional identification of low thyroid function,[8 (V)] but a low BEI after sudden weight gain or an acute respiratory infection did not rate as identifying.[8 (IV)] Relative to development of progeny (Table III), for the 15 adequately treated hypothyroxinemic women 122 BEI were determined and 47, or 38 per cent, were below the range for euthyroid pregnant women. For the 21 inadequately treated hypothyroxinemic mothers 119 BEI were determined but 71, or 60 per cent, were low. Circulating thyroid autoantibodies were not studied. All the pregnancies were uncomplicated except for low BEI of hypothyroxinemic women, and all neonates had birth weights of at least 2,500 grams. T tests demonstrated no significant differences in maternal IQ's,[10–12] years of education, or chronological age between the women in the two hypothyroxinemic groups adequately and inadequately treated* (see also for recommended thyroid dosage).[6]

The present report includes 210 children born to euthyroid women of diverse ages: 15 born to adequately treated hypothyroxinemic women and 21 born to inadequately treated hypothyroxinemic women. Four and 7 year medical histories, in addition to 7 year pediatric-neurologic examinations, were reviewed to eliminate children who had experienced severe injuries or diseases which would impair development. As a result of this screening procedure, 14 children were excluded from the following analyses (Table II).

*Adequate treatment usually followed the pattern of 180 mg. of Proloid per day after 5 days of 90 mg. per day begun between the gestational weeks 12 and 29. Proloid was generously donated by the Warner-Lambert Research Institute.

Table II. Fourteen 7-year-old progeny excluded from this report because of postnatal medical complications or injuries

Mothers	*No.*	*Cause of exclusion*
Euthyroid:		
Age 15-17 yr.	3	(1) Hypertension
		(1) Auto accident with concussion
		(1) Severe meningitis
Age 18-34 yr.	9	(1) Lead poisoning
		(1) Recurrent tonsillitis, kidney infections, rectal abscess
		(1) Generalized wasting, abdominal distention; deceased at age 8 yr.
		(1) Anemia, scoliosis, weight in fifth percentile
		(1) Congenital cataracts
		(1) Seizures
		(3) Hypertension
Age 35-41 yr.	1	(1) Operations on both eyes; glasses not worn for examination
Hypothyroxinemic:		
Adequate treatment	0	
Inadequate treatment	1	(1) Severe visual abnormality
Total	14	

The children were examined close to their seventh birthdays, usually within 1 month. Examinations were conducted in a pleasant nursery-school milieu. All evaluations were administered and scored without the examiner's knowledge of the mother's thyroid status or the child's developmental, social, or medical history. Among the subtests of the psychological examinations[10–12] were the Wechsler Intelligence Scale for Children, The Bender Visual Motor Gestalt test, and the Goodenough-Harris Draw-a-Person test (Table III). Tactile finger recognition tests and behavior profiles are not included in Table III. Performance on subtests formed the bases for an over-all rating of normal, suspect, or abnormal.

Each of three hypothyroxinemic women was observed during successive pregnancies. For each woman

Table III. Psychological examinations of 7-year-old children*

Mothers	Means					
	No.	*Full-scale IQ*	*Verbal IQ*	*Performance IQ*	*BVMGT† (Bender)*	*Draw-a-Person*
Euthyroid						
Age yr. at prenatal registration						
15-17	51	93.4	91.8	96.0	7.5	89.8
18-24	90§	97.4	93.3	102.5	6.5	93.0
25-34	41	98.5	95.1	102.6	5.8	95.6
35-41	28	97.5	94.8	101.3	5.8	92.3
Total euthyroid	210§	96.6	93.5	100.8	6.5	92.7
Hypothyroxinemic:						
A. Adequate treatment	15	104.5	99.3	109.1	5.7¶	95.7
B. Inadequate treatment	21	91.9‖	91.1‖	95.7‖	8.4	87.9¶
p values—A vs. B, Student's t test		0.0022	0.05	0.0042	0.005	0.0156

*From Fisher, D. A., and Burrow, B. N., editors: Perinatal Thyroid Physiology and Disease (Kroc Foundation Series, vol. 3), New York, 1975, Raven Press, p. 124.

†High score = poorer performance.

‡Per cents expected, WISC Manual, p. 16.

§One value of 37 omitted. Mean would be same.

‖Deaf boy. Leiter IQ = No performance or verbal IQ—No. 20 for verbal and performance IQ.

¶One value omitted because it exceeded the initial mean ± 2 S.D.

it happened that adequate thyroid replacement therapy was given during one pregnancy and inadequate replacement therapy was given in the other pregnancy. Seven-year development of the three sets of siblings and of three sets of siblings in which a retarded child had been born to a woman hypothyroxinemic in a subsequent pregnancy are compared in results.

John Stanbury, M.D., has long been a consultant for our project and has inquired several times about placental insufficiency or weights for the two groups of hypothyroxinemic women. Retrospectively (1974-75), placental weights were retrieved from obstetric records and extreme weights were not verified immediately. The weight of the placenta was an item to be measured as precisely as possible in the Collaborative Study, with a strict protocol as to stripping and use of a balance accurate within 5 Gm. Comments about the placentas or estimated length of gestation were less objective and not used.

Results

Progeny of euthyroid women. In Table III are the mean values for the full-scale IQ's and subtests of 7-year-old progeny born to euthyroid women in increasing age groups. Fifty-one children of young girls aged 15 to 17 years had the lowest scores; the mean full scale IQ of 93.4 was significantly lower ($p < 0.05$ by Student's t test) than the mean for 41 children born to mothers aged 25 to 34 years. In contrast to previously published data of 4-year-old children,[8] (VII) 7-year-old progeny of older women aged 35 to 41 years had only slightly—not significantly—lower scores than progeny of women aged 25 to 34 years. IQ's at 7 years were usually lower than IQ's of the identical 4-year-old children.

Progeny of adequately and inadequately treated hypothyroxinemic women. Fifteen progeny of adequately treated hypothyroxinemic women and 21 progeny of inadequately treated hypothyroxinemic women returned for the 7 year psychological examination. In Fig. 1 six of the 21 progeny of inadequately treated hypothyroxinemic women had 7 year full-scale IQ's below the mean −1 S.D. for progeny of euthyroid women. Conversely, seven of the 15 progeny of adequately treated hypothyroxinemic women had full-scale IQ's above the mean +1 S.D. for progeny of euthyroid women.

At the right of Table III full-scale IQ's of the three groups are divided into ranges 80 or below, 80 to 109, and 110 and above. Per cents in each section are italicized. Inspection of the three bottom rows reveals that: progency of inadequately treated hypothyroxinemic women had the highest per cent (24) of IQ's below 80, and progeny of adequately treated hypothyroxinemic women the highest per cent (47) of IQ's of 110 and above. With the chi-square test the distribution of full-scale IQ's of progeny of

Full-scale IQ's					
<80		*80-109*		*110 & over*	
No.	*%*	*No.*	*%*	*No.*	*%*
	8.9‡		*66.1‡*		*25‡*
10	*20*	36	*71*	5	*10*
9	*10*	64	*71*	17	*19*
1	*2*	34	*83*	6	*15*
1	*4*	24	*86*	3	*11*
21	*10*	158	*75*	31	*15*
0	*0*	8	*53*	7	*47*
5	*24*	16	*76*	0	*0*

euthyroid mothers was significantly different and higher ($0.02 < p < 0.05$) than that of IQ's of progeny born to inadequately treated hypothyroxinemic mothers. We are indebted to Colin White, Professor of Biometry at Yale, for calculating this value. To save space the per cents of performance IQ's 80 or below, 80 to 109, and 110 and above are not included in the table. However, when the same chi-square test was applied to the distribution of the performance IQ's of the children of euthyroid women vs. children of inadequately treated hypothyroxinemic women a significant difference ($p < 0.05$) was found, with the performance IQ's of the children of euthyroid women significantly higher than performance IQ's of children born to inadequately treated hypothyroxinemic women.

Progeny of the adequately treated hypothyroxinemic women obtained higher mean full-scale, verbal, and performance IQ's and better mean scores on the BVMGT (Bender) and Draw-A-Person tests than progeny of inadequately treated hypothyroxinemic women (see Table III). The significant student's t tests are at the bottom of Table III.

Siblings born to hypothyroxinemic women treated once adequately and once inadequately. Each of three hypothyroxinemic women had two children registered in the study with one born after maternal adequate thyroid treatment and one born after inadequate thyroid treatment. In two of the sibling sets, the child from an adequately treated pregnancy was born prior to the sibling of an inadequately treated pregnancy. In the third set, the child of the adequately treated pregnancy was born after the sibling of an inadequately treated pregnancy. Progeny of adequately treated hypothyroxinemic pregnancies obtained mean full-scale, verbal, and performance IQ's of 103.0, 94.7, and 111.7, respectively, whereas the siblings of inadequately treated hypothyroxinemic pregnancies obtained IQ scores of 83.0, 89.5, and 86.0 (these latter two mean scores are based on only two siblings because the Leiter scale was administered to one child). Children from adequately treated pregnancies obtained a better mean BVMGT score (7.3) than their siblings (11.0 suspect), a higher mean DAP score (92.3) than their siblings (81.7), and a higher mean tactile finger recognition score (8.7) than the children from inadequately treated pregnancies (6.0 abnormal). The difference in mean full-scale IQ's is surprisingly large since, in general, siblings tend to have more similar full-scale IQ's; in addition, other scores show marked differences. All progency of adequately treated pregnancies were classified as over-all normal, whereas none of their siblings in the inadequately treated group was classified normal; one of them was classified as suspect and two were classified abnormal. Three other women, who previously had delivered retarded children or a nonviable fetus, asked to come to our clinic in a later pregnancy. They proved to be hypothyroxinemic; adequate doses of Proloid were prescribed early in gestation and continued to term. The results to date are one 8-month-old infant and two 4-year-old children who were developing normally and did not appear retarded by psychological tests.

Placentas. Placental and birth weights for 14 of the inadequately treated hypothyroxinemic maternal-fetal pairs and for 11 of the adequately treated hypothyroxinemic pairs are compared with those for 31 euthyroid controls in Table IV. Control euthyroid mothers were matched as to race, age, and parity, the neonates as to sex and as closely as possible to birth weight—all birth weights were 2,500 grams or more. Mean placental weights, S. D.'s, and ranges of placental weights were similar for the euthyroid control and adequately treated hypothyroxinemic groups. Mean placental weights of 450 grams for the last two groups corresponded with the median placental weight of 400 to 449 grams reported for different races by the Collaborative Study.[14]

In comparison with the above two groups the range of placental weights for the inadequately treated hypothyroxinemic group extended lower and higher. The S. D. was almost twice the S. D.'s for the euthyroid and adequately treated hypothyroxinemic groups. Two of the 14 placentas (14 per cent) of the inadequately treated hypothyroxinemic group exceeded weights of the other 42 placentas in the euthyroid and adequately treated hypothyroxinemic groups, and weighed 616

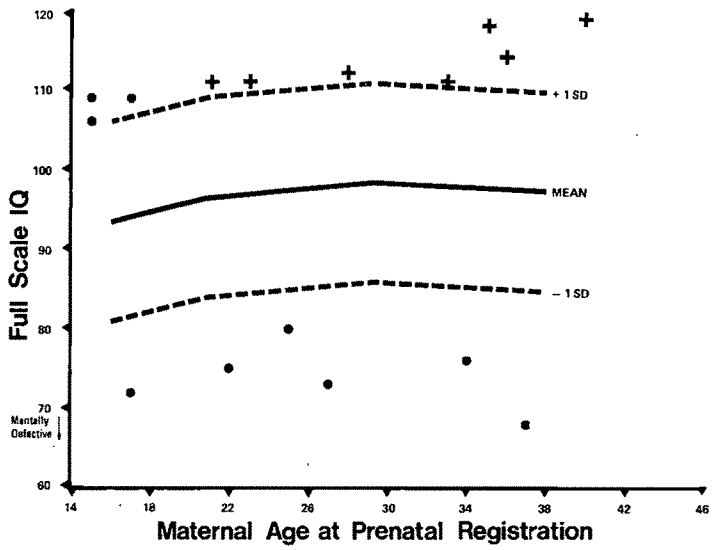


Fig. 1. Full-scale IQ scores of 210 7-year-old children born to euthyroid women plotted against maternal age in years in prenatal registration. Heavy line = mean IQ scores of children born to euthyroid mothers. Broken lines = ± 1 S.D. from mean. S.D. calculated for progeny of euthyroid mothers aged 15 to 17, 18 to 24, 25 to 34, and 35 to 40, and lines smoothed from these values. Solid circles = IQ of child of hypothyroxinemic inadequately treated mother below or above ± 1 S.D. Plus signs = IQ of child of hypothyroxinemic adequately treated mother below or above ± 1 S.D. Additional values have been added since publication. Reproduced with permission from Man, E. B., Jones, W. S., Holden, R. H., and Mellits, E. D.: AM. J. OBSTET. GYNECOL. 111: 905, 1971; from Man, E. B.: Critical Review in Clin. Lab. Sci. by the Chem. Rubber Co., 3: 203, 1972; and from Fisher, D. A., and Burrow, B. N., editors: Perinatal Thyroid Physiology and Disease (Kroc Foundation Series, vol. 3), New York, 1975, Raven Press, Publishers, p. 123.

Table IV. Placental weights and birth weights

Group	No.	*Birth weight*		*Placental weight*			*Birth weight / Placental weight*	
		Mean (Gm.)	*Range (Gm.)*	*Mean (Gm.)*	*S.D. (Gm.)*	*Range (Gm.)*	*Mean (Gm.)*	*Range (Gm.)*
Hypothyroxinemic:								
Inadequate treatment	14	3,265	2,665-4,224	447	±131.8	273-794	6.84	4.64-10.90
Adequate treatment	11	3,222	2,500-3,997	450	±72.3	339-550	7.16	5.37- 9.10
Euthyroid controls*	31	3,226	2,580-4,791	450	±71.0	334-579	7.17	5.39-10.15

*Euthyroid controls matched as to race, age, and gravida of mother and sex of child and if possible birth weight.

and 794 grams. The mothers were, respectively: gravida 1, age 22, white; neonate's birth weight 2,863 grams, birth weight/placental weight 4.64; gravida 8, para 6, ab. 1, age 37, white; neonate's birth weight 3,884 grams, birth weight/placental weight 4.89—one of her surviving six infants weighed only 1,863 grams and two others had minor anomalies. These high placental weights are exceptional even though the Perinatal Collaborative Study suggested that "relatively heavier placentas" with respect to birth weights occur with "increasing age of the gravida and increasing parity."[14]

Data are too limited to permit any hypothesis regarding placental weight and development of the offspring. Of the 21 progeny of inadequately treated hypothyroxinemic women, five had 7 year full-scale IQ's below 80, in the mentally defective range, but for three of those five, placental weights were not recorded. The low Leiter IQ of 76 was associated with a placenta markedly heavier (564 grams) than expected for a male infant with birth weight of 2,665 grams and a birth weight/placental weight of 4.73. When all placental weights were plotted against birth weights the same line pertained for the control and adequately

treated hypothyroxinemic groups, but for the inadequately treated hypothyroxinemic group placental weights fell slightly off the line, with placental weights heavier than expected for birth weight.

Comment

The grant request for this study was submitted 15 years ago, September, 1960. In fact, this was a continuation of research initiated by Peters and Heinemann in 1948.[8] (I, Ref. 1) Techniques had to remain constant for final comparability even though better methods were developed during the program, and future investigators could improve this research project. Serum T3 values are diagnostically significant in difficult thyroidal problems.[4] Fisher[5] has summarized advances developed since 1970 in biochemical diagnosis of thyroid disease. New RIA (radioimmunoassay) methods require only minute amounts of serum, are not affected by iodine-containing contaminants, have "the potential for nanogram (10^{-9}Gm.) to picogram (10^{-12}Gm.) sensitivity."[5] RIA techniques are now available from small blood samples of high-risk pregnant patients and neonates.

Prenatal care of hypothyroxinemic mothers. One group of inadequately treated hypothyroxinemic patients registered prior to establishment of BEI norms for prenatal patients at Providence Lying-In Hospital Clinic and prior to the initiation of the therapeutic program. For the 21 mothers in the inadequately treated group eight registered and were followed in the prenatal clinic from 9 to 17 gestational weeks, four by 20 to 24 weeks, five by 25 to 29 weeks, and only four were as late as 31 to 35 weeks. Consequently, prenatal care was not exceptionally deficient for these women.

Postpartum thyroid status of hypothyroxinemic women. Thyroid status of women who had been hypothyroxinemic during pregnancy was difficult to evaluate. Only about one-third returned for the 6 week postpartum checkup. Another prime interference was the early time for contraceptive medication—often at postpartum discharge from the hospital. Different contraceptive agents alter various thyroid tests. Ramey and associates[15] have reported augmented TSH response to TRH for women on oral contraceptives. Since some contraceptive preparations elevate TBG capacity and thus elevate the BEI, evaluation of BEI 6 weeks postpartum was not prognostic of thyroid underfunction. In relation to postpartum thyroid medication the women were instructed to taper Proloid with complete omission by 6 weeks after delivery. Theoretically, after cessation of replacement therapy, possibly 6 weeks are required before serum thyroxine stabilizes. Considering general prescription of contraceptives and women's objections to a 12 week postpartum checkup, in most instances the postpartum nonpregnant thyroid status was not evaluated. However, four of the adequately treated and three of the inadequately treated hypothyroxinemic women had one or more low postpartum BEI values.

Home environment and socioeconomic status. Home environment and socioeconomic status are undoubtedly significant in the child's performance on psychological examinations. As to maternal attitude and age: maternal ages at prenatal registration were similar in the euthyroid and the two hypothyroxinemic groups. Thirty-seven was the oldest age in the inadequately treated hypothyroxinemic group, but in the euthyroid group the women were older: one aged 41 and four aged 40 years. At 4 years of age of progeny, the Pari test of maternal attitude had been examined with no apparent differences between groups. Mean years of education and IQ's of mothers in the two hypothyroxinemic groups were similar. But maternal stimuli and homes with fatigued, sleepy mothers may have occurred for progeny of hypothyroxinemic women whose thyroid therapy ceased within weeks after parturition. Behar has emphasized that poor home socioeconomic conditions can be caused by poor health.[8] (V)

Biochemical thyroid function tests on infants. A normal neonatal hyperactive thyroid status per biochemical tests has been described by Fisher and Burrow.[3] Tremendous increases in serum TSH, T4, and T3 of the newborn infant within hours after birth are summarized by Larsen with major references to his and Fisher's research.[3] Activity of the term neonate's hypothalamic-pituitary axis confirms need for thyroid hormones in normal development of a human infant. Serum TSH peaks to 80 μU per milliliter ½ hour after birth, eight times cord values.[6] Serum total T3 rises by a 400 per cent increment over cord values at 24 hours[3] and serum free T3 is above adult values at 3 days and 6 weeks after birth.[3] Larsen's group has emphasized that adult values for serum thyroid hormones are inadequate and inappropriate as normal ranges of thyroid hormones of infants and children.

That children should be tested for thyroid dysfunction is suggested by a survey study of 5,179 children of whom 201 (39/1,000) were found to have some thyroid abnormality. Only six of the 201 had been so diagnosed previously. The survey had been initiated to examine 1,378 children in the fallout radiation areas of Utah and Nevada. In Utah and Arizona, where iodine deficiency has been corrected, 3,801 control children were examined. The control groups had as high an incidence of thyroid abnormalities—no statistical dif-

ferences—as the exposed children in the fallout area.[16]

Animals, gestation, and thyroid interrelationships. No references have been made to the voluminous and inappropriate literature on the effects of thyroid hormone during gestation of animals. Maturation of newborn animals varies with the species—newborn mice almost inactive vs. a colt or foal which can run around the field soon after birth. Placentation in sheep differs significantly from human placentation. Data on pregnant sheep and other animals are not directly related to gestation and the thyroid gland in women. Research studies with *Macaca mulatta* monkeys are more pertinent and were mentioned.[8] (II) In referring to animal experimentation and the thyroid gland, all articles should be studied minutely to determine whether doses of thyroid hormones or antithyroid drugs are excessive or correctly correlated to physiologic doses for animals of that age and weight.

Summary

In the problem of adequate development or lifetime retardation, thyroid hormones have been recognized as essential for maturation of the central nervous system.[1] The reason for this is not known. Possibly in our studies maternal metabolism or placental physiology improved when a hypothyroxinemic woman was taking adequate thyroid replacement therapy. This report deals only with children who had been born at term and who were considered normal neonatally. In our studies at Providence Lying-In Hospital Prenatal Clinic, reproductive histories of hypothyroxinemic women included a lesser incidence of surviving neonates weighing at least 2,500 grams and a higher incidence of abortions, prematurity, stillbirths, major anomalies, and progeny with subsequent retardation.[8] (VI) What is the role of maternal thyroid hormones in successful reproduction?

This was a continuing, multidisciplinary investigation. Appreciation is given to many staff members at Providence Lying-In Hospital and at the Brown University Child Study Center. Names of associates are many, but Miss Myrtle A. Mitchell, Mrs. Helen M. Haeseler, and Mrs. Ruth Tennant were vital in this study. Dr. Lewis P. Lipsitt, Director of the Child Study Center, Professor of Psychology and Medical Science at Brown University, stimulated and encouraged this research.

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Identification of the cold-insoluble globulin of plasma in amniotic fluid

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A fetal and adult plasma protein known as the cold-insoluble globulin (CIg) of plasma has been identified in amniotic fluid. Its concentration relative to the total protein in amniotic fluid is several times higher than that in adult or fetal plasma, suggesting that it arises from amniotic tissues.

THE COLD-INSOLUBLE globulin (CIg) of plasma is a major component of human plasma of uncertain biologic function. It was originally believed to be a modified form of fibrinogen[1] but it has now been clearly shown to be a unique plasma protein, antigenically distinct from fibrinogen and other plasma proteins.[2, 3] CIg is a glycoprotein having a molecular weight of 450,000; it is composed of two disulfide-bridged, apparently identical chains, each having a molecular weight of 220,000.[3]

A clear picture of its metabolism has not yet emerged, but several observations permit a partial portrayal. Tissue culture and related studies of fibroblasts of human and chicken origin indicate that CIg is antigenically identical with a specific fibroblast surface protein termed fibroblast surface antigen (SF-antigen)[4]; its production seems to be restricted to the fibroblast and certain primitive embryonic cells of mesenchymal origin.[5] CIg in plasma forms complexes with fibrinogen or modified forms of fibrinogen.[1, 6, 7] It is incorporated into fibrin during transglutaminase (plasma Factor XIIIa)–catalyzed cross-linking[8]; participation in clot formation in this way probably accounts for the fact that the level of CIg is lower in serum than it is in plasma.[2] During recurrent cholestasis of pregnancy, CIg levels were markedly elevated,[9] suggesting that an important metabolic pathway for this protein may involve excretion by the liver.

CIg is also found in platelet lysates[2] but it is absent from spinal fluid.[10] To our knowledge its presence in other biologic fluids has not been determined. The present report summarizes our finding that substantial quantities of CIg are present in amniotic fluid.

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Materials and methods

Amniotic fluid was obtained by amniocentesis during the second trimester of pregnancy. Cells and cellular debris were removed by centrifugation prior to analysis. Individual samples as well as a pool comprised of more than 60 individual donors were studied. Citrated adult and fetal cord plasma samples were provided by Dr. Dennis Galanakis. The total protein in these samples was determined by the method of Lowry and associates[11] with a bovine serum albumin standard. Rabbit antiserum specific for human CIg was prepared as previously reported.[2] Immunodiffusion was carried out by standard procedures. Quantitative determinations of CIg levels in biologic samples were made by electroimmunoassay[12] as previously described.[2] Dodecyl sulfate polyacrylamide gell electrophoresis[13] was performed in gels whose final concentration was 5 per cent. For disulfide bond reduction dithiothreitol (14 mM, final concentration) was added. Electrophoresis was carried out at 6 mA. per gel for 4 hours. Gels were stained with Coomassie brilliant blue.[14] Crossed immunoelectrophoresis[15] into 1 per cent agarose (barbital buffer, pH 8.6) containing anti-CIg serum (0.45 per cent, v/v) was carried out on longitudinally sliced gel sections of samples which had been subjected to dodecyl sulfate gel electrophoresis in

the first dimension. For this procedure to be carried out on slices containing sodium dodecyl sulfate, a 3 mm. layer of 1 per cent agarose containing 1.5 per cent Lubrol PX (Sigma Chemical Co.) was interposed between the acrylamide gel slice and the agarose containing the antiserum, as suggested by Converse and Papermaster.[16] Electrophoresis in the second dimension was carried out on glass slides (7.5 by 5 cm.) at 60 V. for 18 hours. Following this, the plates were washed consecutively with saline, ethylene glycol: ethanol: H_2O (10:20:70, v/v), and water; the slides were then air dried and the precipitin lines which remained were stained with Coomassie brilliant blue.

Results

Immunochemical identification of CIg in amniotic fluid. Immunodiffusion analysis with antiserum to CIg revealed its presence in amniotic fluid (Fig. 1); the precipitation line which formed showed complete identity with the CIg precipitin line produced against adult or fetal plasma (adult and fetal CIg are themselves immunochemically identical by this analysis).

Electrophoretic investigation of amniotic fluid CIg. Further investigation of amniotic fluid CIg was carried out by electrophoresis in 5 per cent polyacrylamide gels containing sodium dodecyl sulfate. Amniotic fluid possesses a band with the same anodal migration rate as the major band of adult plasma CIg (molecular weight 450,000[6]; arrows, Fig. 2).

Crossed immunoelectrophoresis of dodecyl sulfate–containing gels of amniotic fluid (Fig. 2), although showing the presence of CIg in this region of the gel, revealed a broad biphasic immunoprecipitin reaction; the distribution indicated the presence of more rapidly migrating material bearing CIg antigenic determinants. By constructing a calibration curve based upon the anodal migration rate and molecular weight of known proteins in amniotic fluid (i.e., IgG, transferrin, albumin) the apparent molecular weights of the two immunoprecipitin peaks were estimated to be approximately 220,000 and 125,000, respectively.

Quantitative aspects. The mean concentration in eight single donor samples of amniotic fluid was 0.08 ± 0.02 Gm. per liter (Table I). A pool of 60 individual amniotic fluid specimens yielded a value of 0.07 Gm. per liter (Table II). CIg levels in adult and fetal plasma were 0.25 and 0.12 Gm. per liter, respectively. If the foregoing data are expressed as a proportion of the total protein in the sample (Table II), it becomes apparent that the relative concentration of amniotic fluid CIg is higher than either adult or fetal plasma CIg. The implication of these findings is considered in the comment section below.

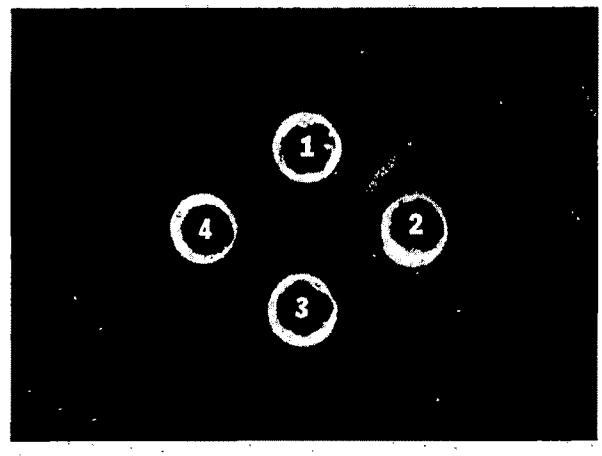


Fig. 1. Agarose gel immunodiffusion analysis of plasma or amniotic fluid. The wells contain *(1)* anti-CIg antiserum, *(2)* pooled adult plasma, *(3)* pooled amniotic fluid, *(4)* pooled fetal plasma.



Fig. 2. Dodecyl sulfate polyacrylamide gel electrophoresis of amniotic fluid and adult plasma CIg in 5 per cent gels (anode is at the bottom); crossed immunoelectrophoresis of the amniotic fluid gel into agarose gel containing anti-CIg serum is shown to the left of the acrylamide gels. The agarose immunoprecipitin pattern is aligned with the stained gel so that it corresponds to the position occupied by a duplicate gel slice during electrophoresis (anode to the left). The horizontal arrows point to the high molecular weight CIg band.

Table I. Determination of the CIg level in single-donor amniotic fluid samples

Sample No.	*Concentration (Gm./L.)*
1	0.08
2	0.09
3	0.07
4	0.06
5	0.10
6	0.09
7	0.06
8	0.10
Mean	0.08
S.D.	±0.02

Table II. CIg levels of pooled samples*

	Concentration	
	Gm./L.	*per cent total protein*
Amniotic fluid	0.07	1.2
Adult plasma	0.25	0.3
Fetal plasma	0.12	0.2

*Values shown are the average of two separate determinations.

Comment

The availability of a specific antiserum prepared against purified human plasma CIg has made possible its identification in amniotic fluid. Since most antisera to human plasma or serum do not react with CIg,[2] it is not surprising that investigations relying upon immunochemical identification of amniotic fluid proteins[17–19] have failed to detect it. Furthermore, studies of amniotic fluid which have focused on proteins unique to this fluid have used antisera to amniotic fluid which had been absorbed with maternal serum.[18, 20, 21] This procedure, by removing or markedly reducing antibodies to CIg, were they present, would also have precluded its detection.

Considerable heterogeneity on the basis of size was demonstrated by crossed immunoelectrophoresis of amniotic fluid (Fig. 2). The size distribution is similar to that found in purified adult plasma CIg which, in addition to the major high molecular weight band (arrows, Fig. 2) shows several minor bands—all possess the CIg antigenic determinant(s) (unpublished results). Size heterogeneity in plasma or in amniotic fluid may reflect different sites of proteolytic attack resulting in release of CIg from the surface of the parent cell; it may also reflect a progressive proteolytic process such as occurs to plasma fibrinogen in the circulation.[14]

The following considerations suggest that amniotic fluid CIg is probably derived from fetal amniotic rather than from maternal or other fetal tissues. There is an inverse relationship between molecular size and the relative concentration of amniotic fluid proteins derived from the maternal circulation.[22–24] Large plasma proteins like β lipoprotein, α_2 macroglobulin, IgM, and fibrinogen are absent[19, 25, 26]; ceruloplasmin and IgG are present at levels well below those in circulating maternal or fetal plasma.[18] Considering its size (most material has a molecular size in excess of 220,000), if amniotic fluid CIg were derived by passive filtration, its relative concentration would be considerably lower than that in the plasma from which it was derived. Since the data show (Table II) that its relative concentration is actually several times higher than that in maternal or fetal plasma, this indicates that most, if not all CIg in amniotic fluid must originate from amniotic tissues. The observation that fibroblast-like cells grow in tissue cultures of amniotic fluid cells[5] provides a candidate cell for its production. This subject is currently under active investigation.

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Estimation of fetal weight by ultrasonic abdominometry

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The fetal abdomen was measured with an ultrasonic contact scanner in order to correlate abdomenal circumference and birth weight. A sample of 134 measurements was used to calculate a standard graph, which was then tested against a subsequent 280 measurements, giving a mean estimation error of 105 Gm. Head-to-abdomen circumference ratio measurements were used to assess the type of growth retardation.

IT IS GENERALLY accepted that any method that could accurately predict fetal weight would be of considerable help in the recognition of fetal growth retardation and in the management of labor. Methods utilized so far have been based on radiography, clinical assessment, and ultrasonic cephalometry. From ultrasonic studies it would appear that attempts to predict birth weight from a single biparietal diameter measurement near term are of little value and very often are as good as estimation made from palpation of the uterus.

Willocks and associates[1] found that in 67 per cent of cases the fetal weight could be estimated to within ±454 Gm., Thompson and associates[2] found that in 68 per cent of cases it could be estimated to within ±480 Gm., and Kohorn[3] estimated in 68 per cent of cases to within 490 Gm. From these results it was generally concluded that a single biparietal diameter reading was of value in fetal weight prediction. These figures, however, seem less impressive if we consider the statement by Lind[4] that, if an observer did not examine the patient at all, but simply guessed each fetal weight as 3.3 kilograms, he would be within 454 Gm. of the true weight in 70 per cent of 500 normal cases at term. From this it is clear that, to assess the value of any method of fetal weight prediction, it is important to include in the study the babies at the upper and lower limits of normal. In none of the previously mentioned ultrasonic studies was there a significant number of babies below 2.5 kilograms. Recently Campbell,[5] in a series which included 211 babies below 2.5 kilograms, found that birth weight could be predicted to within 406 Gm. in 68 per cent of cases. In our series of 2,084 babies (201 of low birth weight) we could predict the weight to within 420 Gm.[6] At the extremes this represents an improvement compared to predictions made from abdominal palpation but in practical terms it is not acceptable. Clearly, ultrasonic cephalometry is inadequate for weight prediction. Another technique is required that can predict birth weight from a single measurement during the last 4 weeks of pregnancy but not more than 2 days before birth.

The present study was undertaken to assess the degree of reliability of estimation of fetal weight by ultrasonic measurement of the fetal abdomen circumference at the level where the umbilical vein crossenters the liver.

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Materials and methods

A total of 280 patients with singleton pregnancies were examined. Only measurements made within 2 days of delivery were included in order to avoid significant discrepancy due to growth of the fetus in the interval between measurement and delivery. The machine used was a Diasonograph NE 4102, with the ultrasonic caliper speed set to 1,600 m. per second.

The technique of fetal abdominometry involves a serial longitudinal scan in order to determine the correct level and angle for performance of a circumference measurement of the fetal abdomen. The angle of inclination of the cross-sectional plane is generally taken at right angles to the long axis of the fetus. The aparatus is then changed to a transversed (Fig. 1) position, tilted to the previously measured angle, and cross-sectional scans are done until the umbilical vein is identified, passing through the liver. In a normal vertex position this is relatively easily found. In a

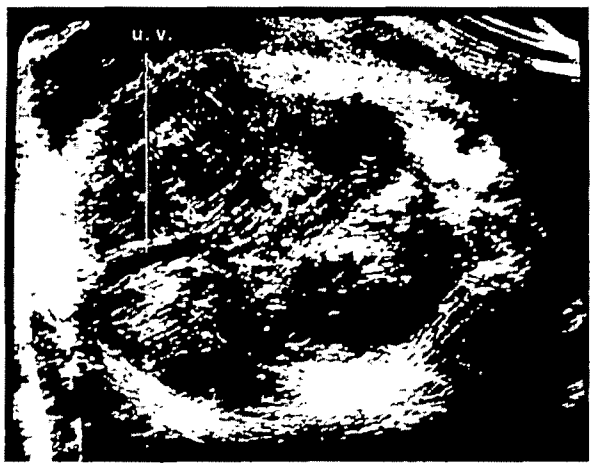


Fig. 1. Transverse section of the fetal abdomen and the umbilical vein *(u.v.)* surrounded by the speckling from the fetal liver.

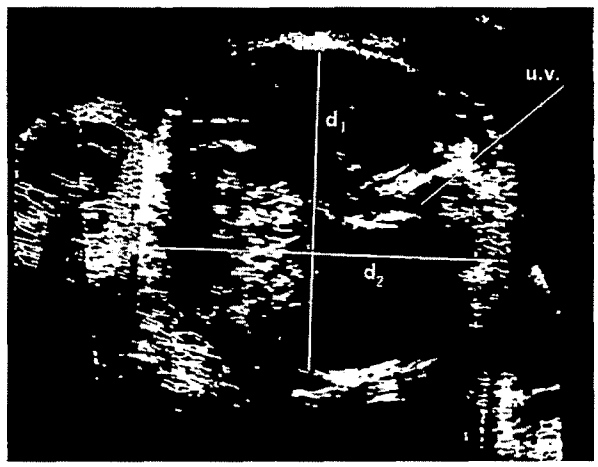


Fig. 2. Circumference measurement using the longest and the shortest diameter of the cross-section. $C = (d_1 + d_2)\ \pi/2 = (d_1 + d_2) \times 1.57$.

breech or transverse position the right plane is much harder to find. It requires an experienced operator or it can be a source of error. Circumference measurements are performed from the largest possible image on the screen. As can be seen from Fig. 2, we measure two diameters (the largest and the smallest) and calculate the circumference, i.e. we approximate the circumference by an ellipse. The two diameters are usually measured directly from the screen with the bright-up calipers.

Stimulated by the investigations of Campbell[5] and Holländer,[16] we performed measurements of the head-to-abdomen circumference ratio, measuring the head circumference at the normal BPD measurement level in the same manner as the abdomen circumference.

Results

In the first part of our study we plotted 134 circumference measurements against actual birth weight. In Fig. 3 the dependence of our circumference measurements on birth weight is shown. Only measurements performed within 2 days of delivery were used. The circumference in the graph is the circumference of the fetal abdomen as previously described. In a subsequent 280 measurements we checked the graph in Fig. 3 by taking the mean value from the graph as the expected weight and calculating the error of the prediction as the difference between our prediction and the actual weight. The results are given in Table I.

In 830 of the cases the difference between the actual and expected weight was within ±150 Gm. and in 94 per cent within ±250 Gm. The mean error was 105 Gm. and the maximum error 310 Gm. The prediction of birth weight was as proficient at the extremes of birth

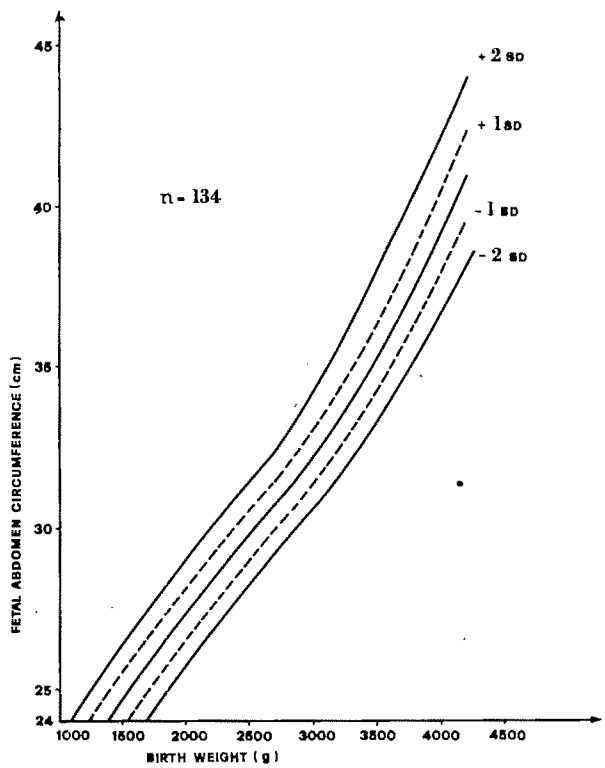


Fig. 3. Graphic representation of the dependence of abdominal circumference of the fetus on weight at delivery during the last 4 weeks of gestation. The graph was calculated from 134 cases measured within 2 days from delivery.

weight range as in the middle. Among the whole set there was one odd result, producing an error of 620 Gm. It was a breech presentation and by postpartal measurement the ultrasonic measurement result was proved to be an obvious error and in view of the

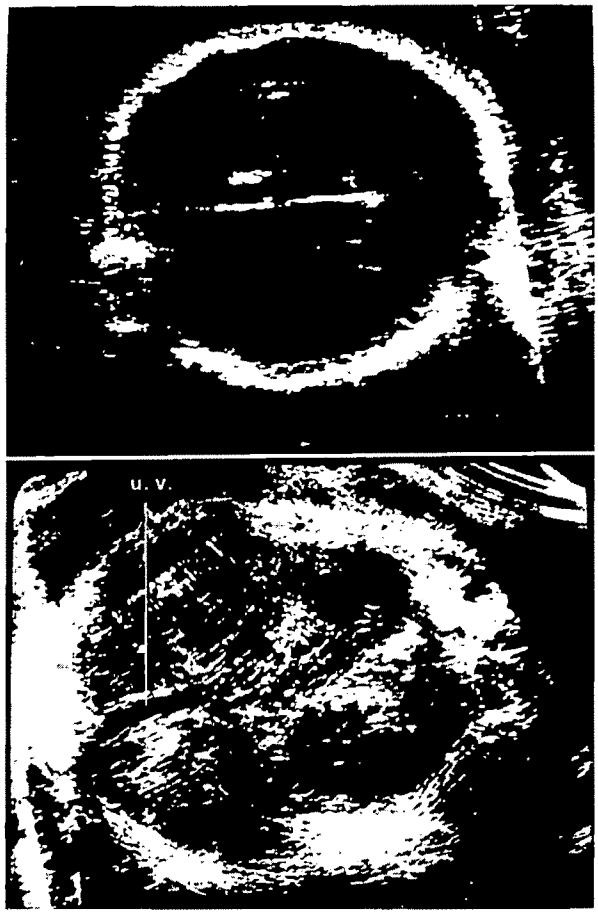


Fig. 4. Echograms showing head (above) and abdomen (below) at 37 weeks of menstrual age. The abdomen circumference is now slightly larger than that of the head and will continue to increase in relation to the head circumference toward term (*u.v.* = umbilical vein).

homogenity of the rest of the results this one was discarded.

The fetal weights ranged from 1,300 to 4,850 Gm.

After the abdomen circumference measurement started to show its value we undertook 200 measurements of head-to-abdomen circumference ratio. During the second trimester this ratio is greater than one but by 36 to 37 weeks, because of the rapid accumulation of subcutaneous fat and soft tissue during the later part of pregnancy, the circumference of the abdomen has caught up with that of the head (Fig. 4), and during the last 4 weeks it is almost invariably greater. However, in most cases of growth retardation this reversal of the head-to-abdomen circumference ratio does not occur and in Fig. 5 it can be seen that 18 out of 19 babies born below the tenth percentile weight for gestation had ratios of one or greater; conversely, 177 out of 181 babies of normal weight (97.5 per cent) had ratios of less than one.

Table I. Difference between actual and expected weights*

Difference (Gm.)	*No. of patients*	*Per cent*
± 50	42	15
± 50 to ± 100	106	38
± 100 to ± 150	84	30
± 150 to ± 200	30	11
± 200 to ± 250	13	4.5
over 250	5	1.5
Total	280	100

*Mean error = 105 Gm.; maximum error = 310 Gm.

Comment

The decision to induce labor before term in complications of pregnancy is to a certain extent influenced by the assessment of fetal size. In cases where the weight of the baby is about 2,000 Gm. errors of more than 400 to 500 Gm. may critically affect the baby's chances for survival if a wrong decision is made. In the same way any method that provides reliable information on fetal size and which can be used to screen large number of patients will be a potent factor in the reduction of perinatal death and morbidity. Despite the fact that the biparietal diameter is the most accurate linear measurement that can be obtained during the antenatal period, cephalometry is not particularly helpful in estimating fetal weight. Many workers have attempted to make predictions of the birthweight by palpation of the maternal abdomen, because clinical estimation after abdominal palpation is the commonest method of assessing fetal weight in utero. Loeffler[7] found that 79.9 per cent of estimates were within 1 pound of the baby's weight. Johnson and Tosach[8] calculated fetal weight from the distance between symphysis pubis and uterine fundus and the station of the fetal head. They reported an accuracy of ±240 Gm. in 50.5 per cent of 200 examined cases. Poulos and Langstadt[9] estimated fetal weight according to the volume of uterus with an accuracy of ±250 Gm. in 68 per cent of estimations. Their material consisted of 45 cases with no babies below 2,500 Gm. More recently Ong and Sen[10] estimated in 82.5 per cent of cases within ±1 pound but there was a tendency to overestimate in the lower range and underestimate in the higher range. The work of Beazley and Kurjak[11] shows a prediction of fetal weight after 36 weeks' gestation to within ±500 Gm. in 75 per cent of cases.

Prediction of birth weight by ultrasonic measurement of fetal body sections was recommended by Thompson and associates,[2] Garret and Robinson,[12] Hansmann and associates,[13] and Campbell.[14] Thompson and associates,[2] using a contact scanner, took sections of the fetal thorax and by means of a

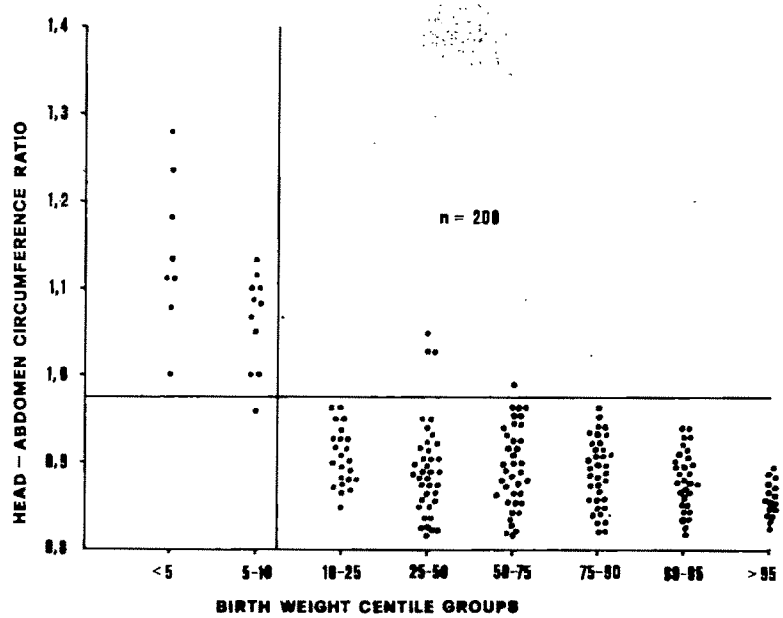


Fig. 5. Relationship between the head-to-abdomen circumference ratio and the birth weight centile groups in 200 cases measured on 2 days prior to induction of labor or elective cesarean section.

formula based on the maximum and minimum measurements were able to predict the fetal weight within ±500 Gm. of the actual weight in 80 per cent of babies. Hansmann and associates[13] took circumference measurements of the fetal thorax at right angles to the long axis of the fetus. We followed Campbell's[14] suggestion of taking a lower level across the upper fetal abdomen on the level of umbilical vein. As the fetal liver is the most severely affected organ in cases of type II growth retardation[15] we also feel that this section is of greater importance in the assessment of fetal nutrition.

The fetal abdomen-to-head circumference ratio could be a valuable means of assessing fetal nutrition in late pregnancy and in addition may provide a simple method of distinguishing between wasted and stunted growth-retarded babies.

Finally, we believe that for detection of a small-for-dates fetus from a single ultrasonic examination in late pregnancy the fetal abdomen circumference measurement could be a method of choice. It is our practice to perform this measurement in the majority of patients undergoing induction of labor or elective cesarean section.

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Hydramnion and fetal renal anomalies

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Four instances of hydramnion associated with renal anomalies are reported: two patients had obstructuve uropathies and two had a neoplastic type of renal dysplasia. In two infants water concentration tests revealed a defect in water-concentrating ability. It is postulated that the observed hydramnion resulted from fetal polyuria. In patients with unexplained hydramnion a search for renal anomalies is indicated.

RENAL ANOMALIES are very rarely mentioned in surveys of hydramnion[1–4] in contrast to the well-established renal anomaly–oligohydramnios association.[5–7] We report here four neonatal patients with renal anomalies who were delivered after pregnancies complicated by polyhydramnios. Clinicopathologic observations and postnatal renal function studies provide data which suggest that the hydramnion was caused by fetal polyuria.

Case reports

Case 1. This male infant was born to a healthy woman, gravida 5, para 4. 22 years of age. The pregnancy was uncomplicated and delivery occurred after 41 weeks' gestation. After rupture of the membrans, 6 L. of amniotic fluid were collected. Parturition was otherwise normal. The Apgar score was 9 at 1 minute, the birth weight was 4,060 grams, and the head circumference was 37 cm. The previous sibling, a female, weighed 3,490 grams after 39 weeks' gestation.

Routine physical examination on the first day revealed a mass in the left loin. Intravenous pyelography on the third day showed left hydronephrosis with moderate dilatation of the calyces and pelvis; the ureter was not dilated. On the eighth day a water concentration test was performed and the results are given in Table II. Blood urea and electrolyte values were normal and urinalysis was negative.

Pyeloplasty was performed on postnatal day 20. The subsequent course was normal and repeat pyelography showed improvement in the hydronephrosis. The water concentration test at the age of 5 weeks (Table II) also showed a reversion to normal.

Comment. This infant with a unilateral partial obstructive uropathy had impaired renal concentrating ability of water. There was no other obvious explanation for the hydramnion.

Case 2. This male infant was the product of a healthy 24-year-old mother, gravida 1, para 1. The pregnancy was normal. Parturition after 41 weeks' gestation was complicated by polyhydramnios: 4.5 L. of fluid were measured. The umbilical cord was wound around the neck three times and the cord was elongated (130 cm.). There was a single umbilical artery.

The Apgar score was 9 at 1 minute, the birth weight was 3,300 grams, and the head circumference was 32 cm. Physical examination revealed a distended, wrinkled, and toneless abdominal wall and macropenis. On palpation soft, elongated, tortuous masses were felt, mainly in the loins and lower abdomen.

Constant dribbling micturition was observed postnatally. The blood urea value was 10 mg. per 100 ml. on the first day and rose to 27 mg. per 100 ml. 3 days later. A urinary tract infection developed and the infant died at the age of 6 days with septicemia.

Autopsy revealed stenosis of the penile urethra, dilatation and hypertrophy of the urinary bladder, and bilateral ureterohydronephrosis. There was no ascites. Additional findings included anorchidism and absence of abdominal muscles.

Comment. This infant had a partial obstructive uropathy (prune-belly syndrome) and polyuria. There was no other obvious cause of polyhydramnios.

Case 3. This male neonate was the fifth affected child in a sibship of six with a unique syndrome of renal hamartomas, nephroblastomatosis, and gigantism.[8] He was born, after an uncomplicated pregnancy of 40 weeks' gestation, by breech delivery. The quantity of amniotic fluid was not measured as membrane rupture occurred before admission. There was a record of

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Table I. Clinical, laboratory, and pathologic correlates of fetal renal anomalies and hydramnion

	Case 1: Unilateral hydronephrosis	*Case 2: Bilateral hydronephrosis*	*Case 3: Nephroblastomatosis*	*Case 4: Nephroblastomatosis*
Amniotic fluid volume (L.)	6	4.5	0	+++*
Amniotic fluid dilution (mOsm./L.)	0	0	0	124
Neonatal polyuria	+	+	+	+
per cent weight loss (third day)	10	12	14	10†
Serum sodium (at 3 days)	155	156	165	148
Renal concentration ability impaired	+	0	+	0
Secondary bilateral hydronephrosis and ureter	‡	‡	+	−

*+, Present; −, absent; 0, not examined.
†Despite pushing fluids.
‡Hydronephrosis and hydroureter were primary.

polyhydramnios in one of the previous affected pregnancies and the mother described the delivery of her only normal child as "dry."

The physical and radiologic findings have been described in a previous publication.[8] The findings relevant to renal function were as follows. (1) At the age of 2 hours the serum sodium was 145 mEq. per liter and the blood urea was 19 mg. per 100 ml. (2) There was a loss of 14 per cent of birth weight at 72 hours despite early feeding. (3) At 72 hours the serum osmolality was 324 mOsm. per liter, serum sodium 160 mEq. per liter, and blood urea nitrogen 65 mg. per 100 ml. The simultaneous urine osmolality was 298 mOsm. per liter. (4) The water concentration test at the age of 6 days (results in Table II) also indicated an impaired ability of the kidney to concentrate urine.

The infant died at the age of 4 weeks. At autopsy nephromegaly with mild nonobstructive hydronephrosis and hydroureter were found. Microscopic examination of the kidneys revealed persistent nephrogenesis, hamartomas, and nephroblastomatosis. Other findings did not give a possible explanation of the polyhydramnios.

Comment. An infant with dysplastic and enlarged kidneys had polyuria postnatally and rapidly developed hyperosmolar dehydration. The urine at that time was inappropriately dilute and further investigation revealed evidence of diabetes insipidus.

Case 4. This younger female sibling of Case 3 was born by breech delivery after 40 postmenstrual weeks. The mother was admitted to the obstetric service before delivery on account of the bad obstetric history. Parturition commenced with spontaneous rupture of the membranes: hydramnion was noted but the volume of the amniotic fluid was not measured. The amniotic fluid osmolality was 124 mOsm. per liter. The birth weight was 3,850 grams. The infant had clinical findings similar to those of the previous siblings.

In view of the experience with the previous sibling, special attention was paid to fluid balance. Polyuria (more than 250 ml. of urine per day with urine osmolarities ranging between 108 and 132 mOsm. per liter) was noted and appropriate fluid replacement was made by gastric tube. Although the infant was maintained in fluid and electrolyte balance, she died on the fourth day of no apparent cause.

Autopsy findings were similar to those of Case 3, with the addition of a nodular Wilms' tumor at the upper pole of the left kidney.

Comment. Like her previous siblings, this infant had hydramnion and postnatal impairment of renal retention of fluid. The amniotic fluid, as well as being increased in volume, was hypo-osmolar compared to normal values (231 to 261 mOsm. per liter for 38 to 41 week gestations).[9]

Comment

The common denominators of the patients with renal anomalies described above are as follows: (1) hydramnion, (2) neonatal polyuria, and (3) laboratory evidence postnatally of impaired ability of the kidney to conserve water (Table I). Additional circumstantial evidence of fetal and neonatal renal dysfunction includes the findings of hypo-osmolar amniotic fluid in one instance, mild nonobstructive hydronephrosis and hydroureter in one patient, and the development of hyperosmolar dehydration in three infants (Table I). Particularly pertinent was the failure of renal concentration of water in case 3 in the first 72 postnatal hours, which occurred in the face of rising values of serum sodium and urea and the administration of fluids. Hansen and Smith[10] observed a rise of urine osmolality to 550 to 600 mOsm. per liter in normal neonates deprived of fluids for 72 hours from birth.

Renal anomalies occupy a small place only in reported series of hydramnion.[1–4] Incomplete documentation of those instances recorded does not permit their interpretation. Whereas hydramnion is relatively common in reports of bilateral nephroblastomatosis[8, 11] and of congenital mesoblastic nephroma,[2, 12, 13] we have found no reports of hydramnion in neonates with congenital hydronephrosis.

Hydramnion has been hypothetically related to fetal

Table II. Six-hour water deprivation tests

	Case 1	*Case 2*	*Case 3*
Age at examination (days)	8	35	6
Weight loss (per cent)	2.5	1.0	5.0
Plasma osmolality:			
Start	284	282	298
Finish	299	281	312
Urine osmolality:			
Start	190	194	123
Finish	193	208	119

renal dysfunction in a number of different conditions. In the parabiotic twin syndrome, the polycythemic recipient twin's propensity to hydramnion has been attributed to increased renal blood flow with resultant polyuria.[14] This hypothesis is based upon the observation of dilated renal tubules in these infants and the postnatal finding of neonatal polyuria.

In anencephalic infants and in pituitary agenesis, hydramnion is associated with dilated renal tubules.[15] The latter was considered to indicate fetal polyuria, possibly due to a lack of pituitary hormone(s), and was invoked as an explanation of the hydramnion.

A similar concurrence of hydramnion and dilated renal tubules has been reported in an infant exposed to acetaminophen in fetal life, a drug known to be toxic to the renal tubules.[16] The finding of impaired renal concentration of water postnatally was considered to provide a possible explanation of the observed hydramnion. Furthermore, the mothers of children with nephrogenic diabetes insipidus occasionally have excess amniotic fluid.[17]

Obstructive hydronephrosis due to incomplete ureteric obstruction is an established cause of impaired water concentration by the kidney, also in childhood.[18, 19] The findings in case 1 (Table II) suggest a causative role of the hydronephrosis in the etiology of the observed hydramnion. The pathogenesis of the impairment of renal water-concentrating ability in case 3 is not clear.

Hydramnion occurs in about 1.5 per cent of deliveries[20] and the cause is undiagnosed in about one quarter to one half of them.[3] The patients presented above together with review of pertinent literature suggest that renal anomalies may have a causative role in the production of some instances of hydramnion by causing fetal polyuria. The implication for the clinician is that the finding of unexplained polyhydramnios should lead to a careful prospective search for causes of renal dysfunction in the infants concerned.

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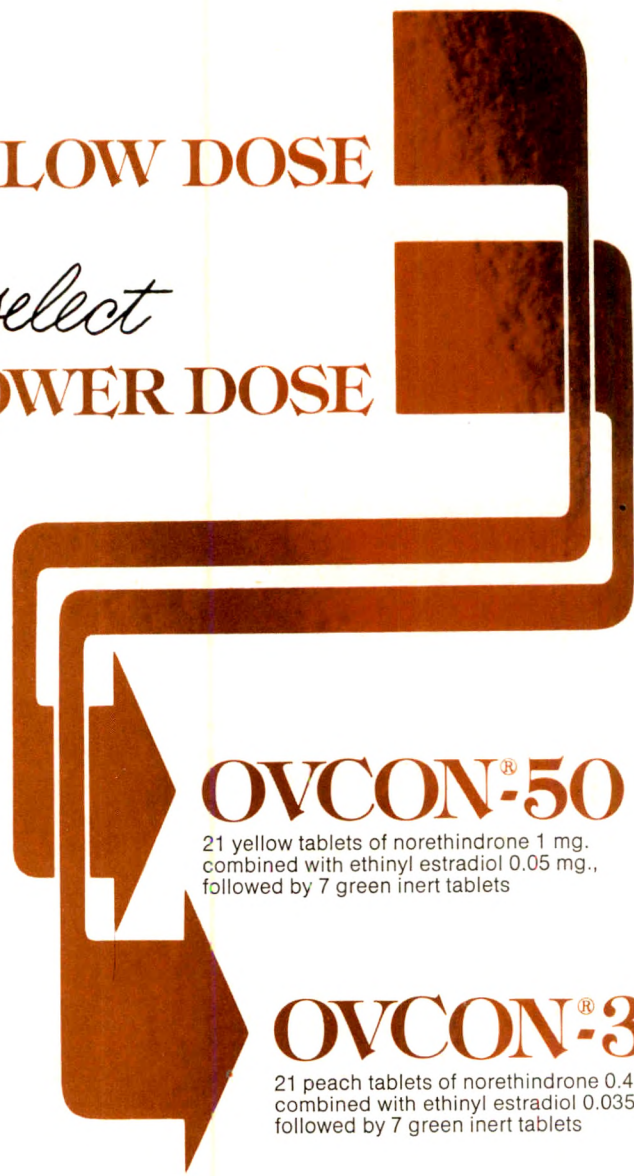
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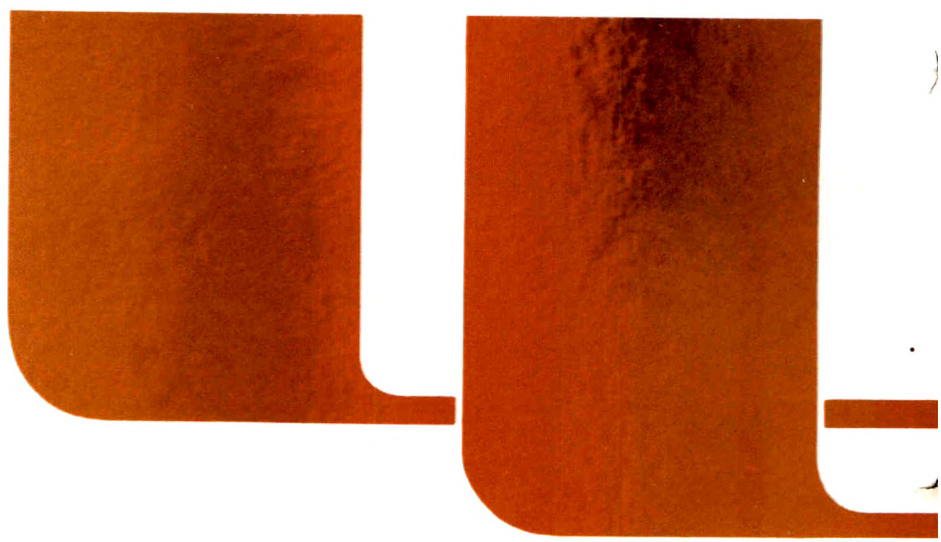
21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

For Brief Summary, please see last page of this advertisement.

One name to remember in combination oral contraceptive effectiveness...

OVCON®

two doses from which to select



providing...

- **effective low-dose contraceptive protection***
- **low incidence of common side effects†**
- **acceptable cycle control†**
- **in-depth clinical studies in widely different populations**

Mead Johnson

OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets

tested in 1,028 women for 9,558 cycles[1]

Although these women represented a wide range of socioeconomic groups with inherent differences in motivation, pregnancy rate (Pearl's formula) was 0.13 pregnancies per 100 woman years due to method failure and 0.75 pregnancies per 100 woman years due to patient failure. This results in a use-effectiveness of 0.88 pregnancies per 100 woman years.

Few women—2.7%—discontinued therapy for cycle-related reasons . . . and these were not necessarily spotting or breakthrough bleeding, but included amenorrhea and what women considered bleeding too little or too much. There was a discontinuation rate of 10.8% for all other on-therapy conditions, which, however, were not necessarily caused by Ovcon-50.

OVCON®-35*

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets

tested in 1,861 women for 20,230 cycles[1]

In these women, with a wide range of backgrounds and motivations, there was effective control of conception. Pregnancy rate (Pearl's formula) due to method failure was 0.41 pregnancies per 100 woman years, and 0.95 pregnancies per 100 woman years were due to patient failure. This results in a use-effectiveness of 1.36 pregnancies per 100 woman years.

There was a higher discontinuation rate —11.6%—for cycle-related reasons with Ovcon-35 than with Ovcon-50, but, again, reasons included any spotting as well as amenorrhea and bleeding too much, too little, or irregularly. On the other hand, the discontinuation rate for all other on-therapy conditions, which were not necessarily related to Ovcon-35, was quite low—7.1%.

1. Data on file, Mead Johnson Laboratories.



OVCON-50 and OVCON-35* offer the advantages of effective low-dose protection and of uninterrupted regimens— 21 active tablets and 7 inert tablets

For Brief Summary, please see following page.

*The effectiveness of Ovcon-35 is somewhat lower than higher-dose combination products.

†See "Special Note" section of prescribing information on last page of this advertisement.

two dosages from which to select

LOW DOSE
OVCON®-50

21 yellow tablets of norethindrone 1 mg. combined with ethinyl estradiol 0.05 mg., followed by 7 green inert tablets.

LOWER DOSE
OVCON®-35

21 peach tablets of norethindrone 0.4 mg. combined with ethinyl estradiol 0.035 mg., followed by 7 green inert tablets.

Special Note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. The effectiveness of OVCON-35 is somewhat lower than higher-dose combination products. Both types provide almost completely effective contraception. The dropout rate for medical reasons due to menstrual disorders and irregularities appears to be higher for OVCON-35 than that observed with higher-dose combination products. An increased risk of thrombotic, thromboembolic and cerebral vascular disease associated with the use of hormonal contraceptives has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations. Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Oral contraception.

Contraindications: Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, or a past history of these conditions; markedly impaired liver function; known or suspected carcinoma of the breast; known or suspected estrogen dependent neoplasia; undiagnosed abnormal genital bleeding; known or suspected pregnancy.

Warnings: If signs of thrombotic and thromboembolic disorders (thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis) occur or are suspected, use of the drug should be discontinued immediately. (Studies indicated a higher risk of these conditions with use of these drugs, not persisting after drug use was discontinued and not enhanced by long-term use.[1-10]) If gradual or sudden, partial or complete loss of vision occurs, or if there is sudden onset of proptosis, diplopia or migraine; or if examination reveals papilledema or retinal vascular lesions, discontinue medication. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11-13] Safety of use in pregnancy has not been established, therefore pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs; long-range effect to the nursing infant cannot be determined at this time. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in short-term as well as long-term users of oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding.

Precautions: A thorough history and physical examination of breasts and pelvic organs should include Papanicolaou smears. (Estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.) If endocrine and liver function tests are abnormal in patients taking these drugs, repeat tests after the drug has been withdrawn for two months. Under the influence of these drugs, pre-existing uterine fibromyomata may increase in size. Some conditions (epilepsy, migraine, asthma, cardiac or renal dysfunction) might be influenced by fluid retention. Observe carefully for such. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Any possible influence of prolonged OVCON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. Diabetic patients should be carefully observed while receiving such therapy. The age of the patient constitutes no absolute limiting factor, although these drugs may mask the onset of the climacteric. The pathologist should be advised of OVCON therapy when relevant specimens are submitted. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. If cholestatic jaundice occurs, OVCON should be discontinued. This condition is more likely to occur in patients with a history of cholestatic jaundice of pregnancy.

Adverse Reactions Observed in Patients Receiving Oral Contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage and gall bladder disease. Suggestive evidence, neither confirmed nor refuted, between use and: neuro-ocular lesions (retinal thrombosis and optic neuritis) and hepatic lesions with or without intra-abdominal bleeding. Known to occur: nausea, vomiting, G.I. symptoms (abdominal cramps and bloating), breakthrough bleeding, change in menstrual flow, spotting, amenorrhea during and after treatment, breast changes (tenderness, enlargement and secretion), mental depression, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals, edema, chloasma or melasma (which may persist), cholestatic jaundice, migraine, rash (allergic). Reported association with use, neither confirmed nor refuted: anovulation post treatment; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; intolerance to contact lenses; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; vaginitis. *May Alter Laboratory Results in:* Hepatic function (increased sulfobromophthalein retention and other tests), coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X, decrease in anti-thrombin III and an increase in norepinephrine-induced platelet aggregability), thyroid function (increase in PBI, and butanol extractable protein bound iodine and decrease in T_3 uptake values), metyrapone test, pregnanediol determination.

References: (1) Royal College of General Practitioners: Oral contraception and thromboembolic disease. J. Coll. Gen. Pract. *13*:267-279, 1967. (2) Inman, W.H.W. and Vessey, M. P. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women in child-bearing age. Brit. Med. J. *2*:193-199, 1968. (3) Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease: A further report. Brit. Med. J. *2*:651-657, 1969. (4) Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. Thromboembolism and oral contraceptives: An epidemiologic case-control study. Amer. J. Epidem. *90*:365-380, 1969. (5) Oral contraception and increased risk of cerebral ischemia or thrombosis. New Eng. J. Med. *288* (17):871-877, 1973. (6) Oral contraceptives and stroke in young women. JAMA *231*(7):718-722, 1975. (7) Boston Collaborative Drug Surveillance Programme. Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumours. Lancet *1*:1399-1404, 1973. (8) Oral Contraceptives and Health. A summary of an interim report from the oral contraception study of the Royal College of General Practitioners, May, 1974. (9) Vessey, M. P., Doll, R., Fairbairn, A. S., and Glober, G. Post-operative thromboembolism and the use of oral contraceptives. Brit. Med. J. *3*:123-126, 1970. (10) Greene, G. R. and Sartwell, P. E. Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am. J. Public Health *62*:680-685, 1972. (11) Nora, A. H. and Nora, J. J. A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch. Envir. Health *30*:17-21, 1975. (12) Janerich, D. T., Piper, J. M., and Glebatis, D. M. Oral contraceptives and congenital limb-reduction defects. New Eng. J. Med. *291*(14):697-700, 1974. (13) Carr, D. H. Cytogenetics and malformations in abortions. Fed. Proc. *30*:102-103, 1971.

Mead Johnson LABORATORIES

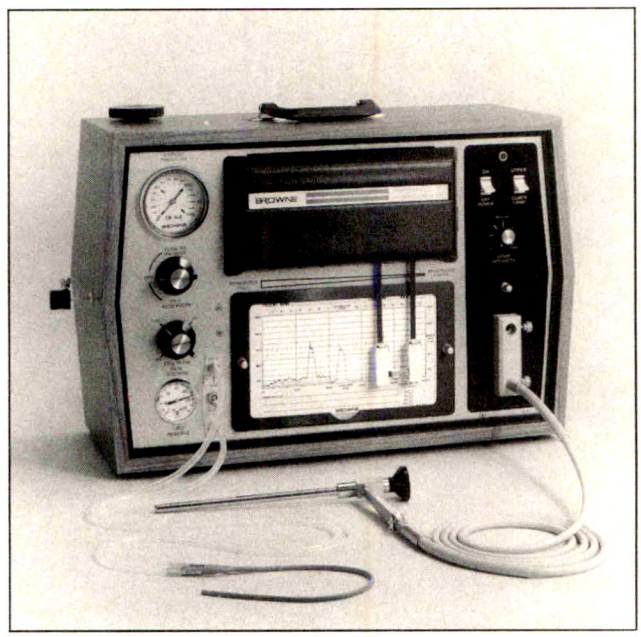
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Lower Urinary Tract Dysfunction... ...Should You Operate?

One of the most critical decisions in any diagnosis today is whether or not to operate. Based on the most comprehensive diagnostic data available, you must make that recommendation. Browne Corporation CO_2 Endoscopy/Cystometry Monitors are designed to add significantly to that data and to present it to you in its most usable form. Consider these features:

Fail Safe Gas Supply System: Delivers CO_2 to patient at selected pre-calibrated flow rates. Three independent safety systems limit pressure and volume supplied during a single cycle. Medical grade cartridge powers both the supply and recording systems.

Automatic Catheter Puller: Synchronized with the recording system to provide direct readout of urethral length and position on the patient chart card.



Fiber Optic Illuminator: Dual 150 watt lamps with variable intensity and selector controls are provided as an option for endoscopy procedures.

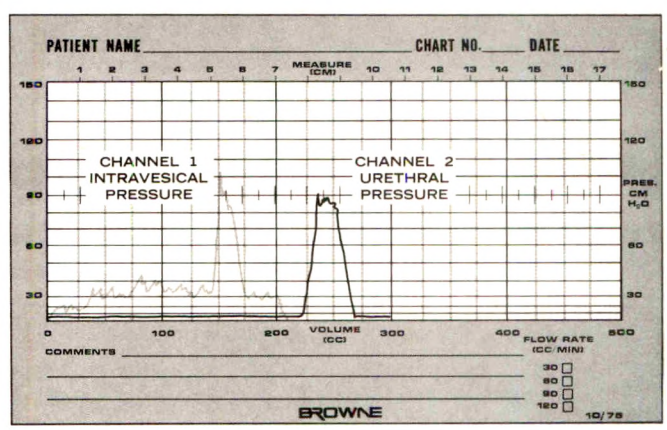
Robertson Urethrascope: Straight ahead, wide-angle field of view. Fully concentric fiber optics assure even illumination. Integral handle with fiber optic and gas fittings simplifies assembly and sterilization. Removable gas sheath, obturator and case included.

Four Function Profile Chart Recorder: Monitors total CMG volume, urethral position, intravesical pressure, and/or urethral pressure. Proprietary design is non-electrical and requires no calibration.

Permanent Record: The exclusive patient chart card provides a clear, concise, retainable record of each procedure for historical and legal purposes. Diagnosis of complex, interacting varibles is often greatly simplified.

The sample card shown at right (one half actual size) is a simulation of a pressure/volume cystometrogram with simultaneous urethral pressure monitoring. Channel one indicates intravesical pressure spasms in excess of 100cm H_2O. Simultaneously, the Monitor's second channel has recorded a normal urethral pressure of 90cm H_2O. This patient's urinary incontinence is probably due to an uninhibited neurogenic bladder. A simple in-office procedure has ruled strongly against surgical candidacy.

Cystometry And Urethral Pressure Catheters: Available in both single lumen and dual lumen versions with calibrated cm markings. Designed to attach directly to the automatic catheter puller.



To arrange a demonstration of the Browne Endoscopy/Cystometry Monitor, please write to us at Browne Corporation, 203 Chapala Street, Santa Barbara, Calif. 93101, or call (805) 963-0371.

BROWNE
CORPORATION

NEW
Natafort®
COMPREHENSIVE PRENATAL VITAMIN FORMULA WITH MINERALS FROM PARKE-DAVIS

NATAFORT is a new, high-potency vitamin preparation with minerals, with special emphasis on the support *you* know is important for your pregnant patients.

- ■ *antianemia factors: iron and folic acid*
- ■ *calcium, 350 mg; and vitamin C*
- ☐ B-complex vitamins: niacinamide, vitamins B_1, B_2, B_6, and B_{12}
- ☐ other vitamins and minerals to help you support your patients' nutritional needs during pregnancy

Prescribe just one NATAFORT Tablet daily.

Each Natafort Tablet represents:

Vitamin A (acetate) (1.8 mg)	6,000 IU*
Vitamin D (ergocalciferol) (10 mcg)	400 IU
Vitamin C (ascorbic acid)	100 mg
Vitamin B_1 (thiamine mononitrate)	3 mg
Vitamin B_2 (riboflavin)	2 mg
Vitamin B_6 (pyridoxine hydrochloride)	15 mg
Vitamin B_{12} (cyanocobalamin) crystalline	5 mcg
Folic Acid†	1 mg
Nicotinamide (niacinamide)	15 mg
Vitamin E (*dl*-alpha tocopheryl acetate) (30 mg)	30 IU
Calcium (as calcium carbonate)	350 mg
Magnesium (as magnesium oxide)	1.7 mg
Iodine (as potassium iodide)	0.15 mg
Iron (as ferrous fumarate)	65 mg

Usual dose: One tablet daily

*IU=International Units

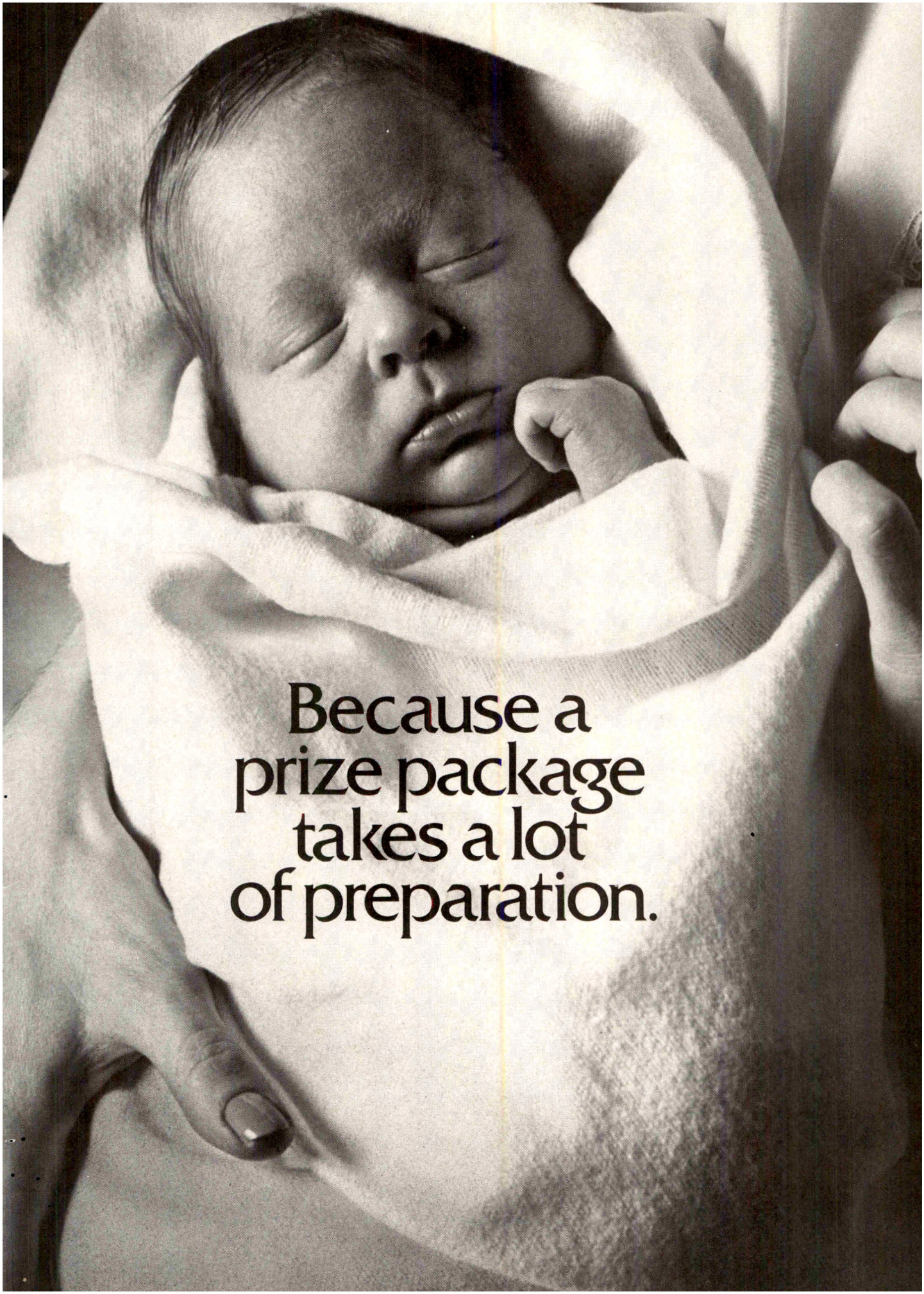
†CAUTION—Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.



PARKE-DAVIS

PD-JA-1955-1-P (5-76)

PARKE, DAVIS & COMPANY
Detroit, Michigan 48232


Because a
prize package
takes a lot
of preparation.

UNIVERSITY OF
SOUTHERN CALIFORNIA
SCHOOL OF MEDICINE

and the

DEPARTMENT OF
OBSTETRICS &
GYNECOLOGY

Announce

THE SIXTH ANNUAL REVIEW COURSE

in

GYNECOLOGY AND OBSTETRICS

The course will be held at the Beverly Hilton Hotel, Beverly Hills, California, Monday thru Friday, October 25-29, 1976. Five days will be devoted to Perinatal Medicine, Gynecology, Gynecologic Oncology, Endocrinology and Infertility and Pathology. The tuition is $250.00. Registration closes October 4, 1976.

Inquiries concerning the program should be addressed to:

Associate Dean, USC School of Medicine,
Postgraduate Division
2025 Zonal Avenue, Los Angeles, CA 90033.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

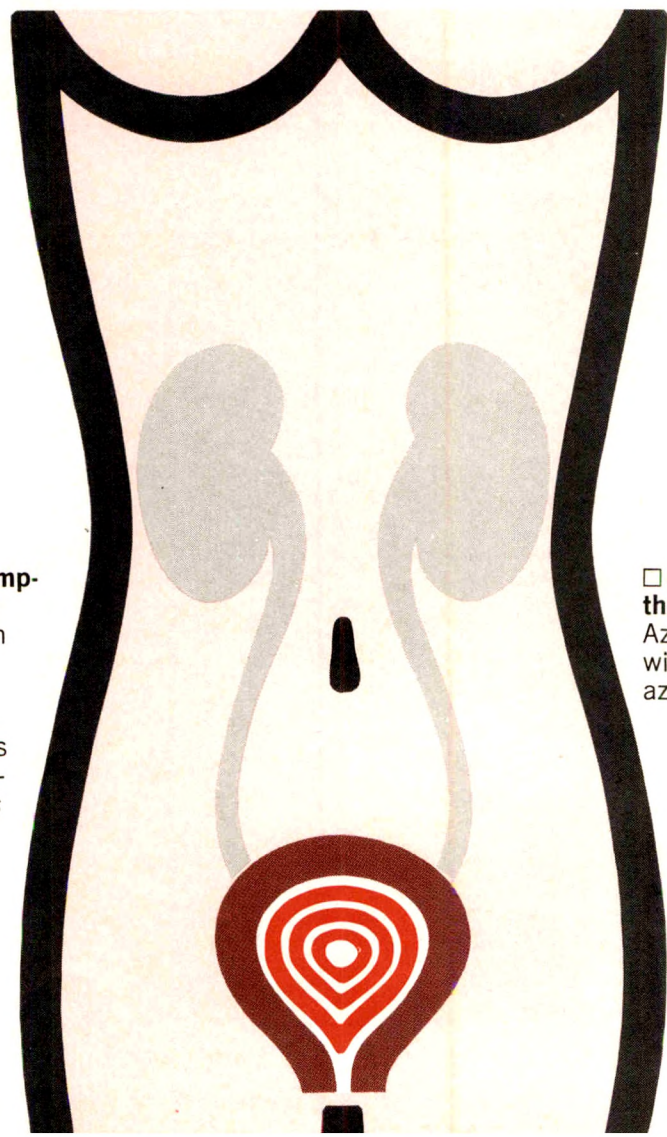
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

When pain complicates acute cystitis*

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain for the pathogens



☐ **Early relief of painful symptoms** such as burning and discomfort associated with urgency and frequency.

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

☐ **Appropriate antibacterial therapy:** up to three days with Azo Gantanol, then 11 days with Gantanol® (sulfamethoxazole).

*nonobstructed; due to susceptible organisms

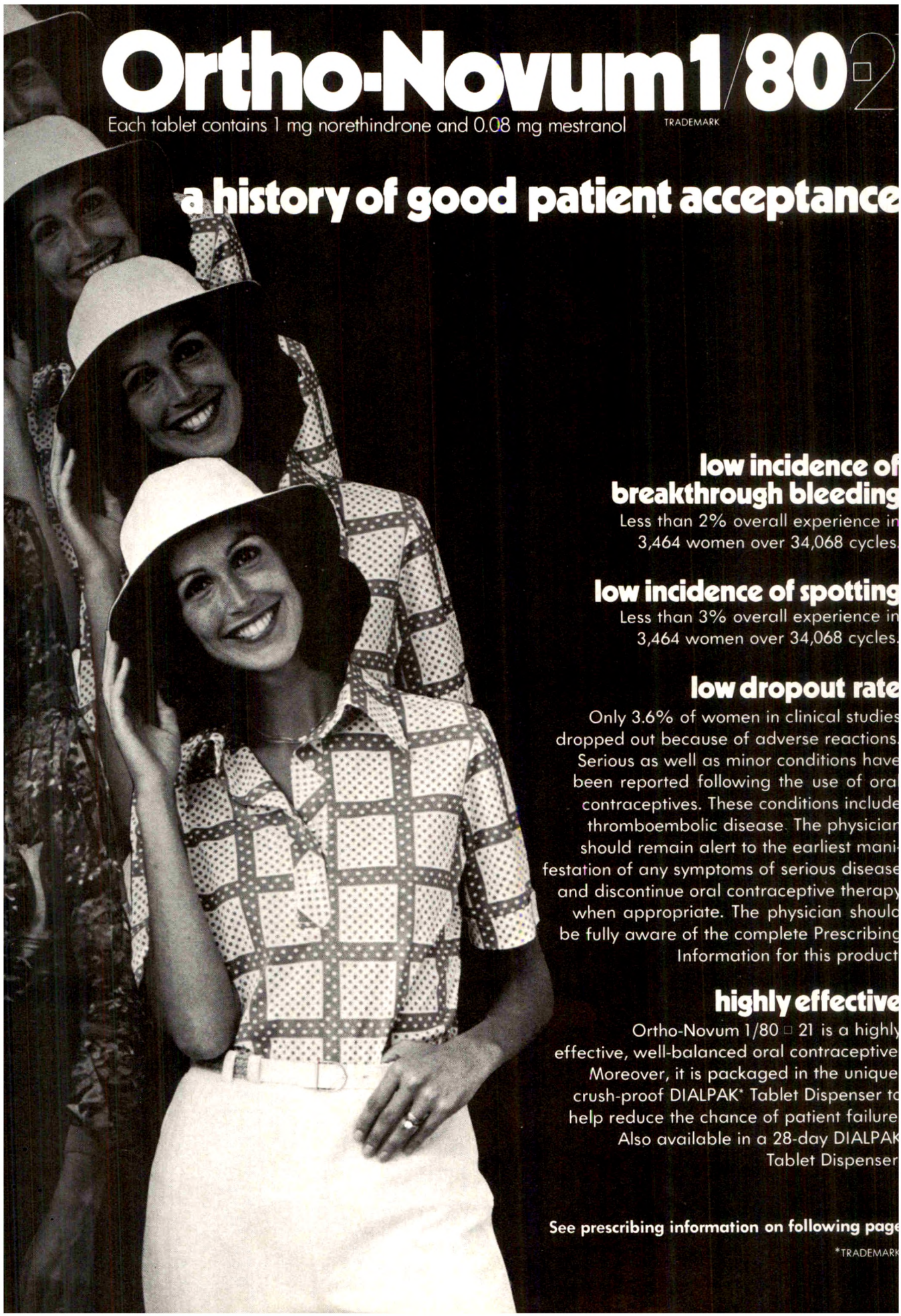
ROCHE



Ortho-Novum 1/80 21

Each tablet contains 1 mg norethindrone and 0.08 mg mestranol TRADEMARK

a history of good patient acceptance



low incidence of breakthrough bleeding

Less than 2% overall experience in 3,464 women over 34,068 cycles.

low incidence of spotting

Less than 3% overall experience in 3,464 women over 34,068 cycles.

low dropout rate

Only 3.6% of women in clinical studies dropped out because of adverse reactions. Serious as well as minor conditions have been reported following the use of oral contraceptives. These conditions include thromboembolic disease. The physician should remain alert to the earliest manifestation of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

highly effective

Ortho-Novum 1/80 □ 21 is a highly effective, well-balanced oral contraceptive. Moreover, it is packaged in the unique crush-proof DIALPAK* Tablet Dispenser to help reduce the chance of patient failure. Also available in a 28-day DIALPAK Tablet Dispenser.

See prescribing information on following page

*TRADEMARK

Ortho-Novum 1/80 21 and 28

TRADEMARK

Each white tablet contains 1 mg norethindrone and 0.08 mg mestranol.
Each green tablet in the 28-day regimen contains inert ingredients.

a history of good patient acceptance



Ortho-Novum 1/80□21 and Ortho-Novum 1/80□28

Description: Each white ORTHO-NOVUM 1/80 tablet contains 1 mg of the progestational substance, norethindrone, together with 0.08 mg of the estrogenic compound, mestranol. Each green tablet in the 28-day regimen contains inert ingredients.

Actions: ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/80□21 and ORTHO-NOVUM 1/80□28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28. Therefore, if such tests are abnormal in a patient taking ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 may mask the onset of the climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during ORTHO-NOVUM 1/80□21 or ORTHO-NOVUM 1/80□28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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GYNECOLOGY

Diagnostic laparoscopy: A prognostic aid in the surgical management of infertility

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Laparoscopy was utilized as the final step in the infertility investigation of 155 indigent patients. Unnecessary laparotomy was avoided in 72 (46 per cent) of these patients. Depending upon the endoscopic findings, the presence of additional infertility factor(s) either positively or negatively affected prognosis. With the same anesthetic, 83 (54 per cent) of the 155 patients underwent conservative infertility operations. Unless even greater selectivity can be achieved by prior diagnostic laparoscopy, the postoperative term pregnancy rate (11 per cent) does not justify infertility operations in a population prone to pelvic inflammatory disease, particularly in those individuals with other infertility factors.

EXTENSIVE ADHESIVE and obliterative pelvic disease will adversely affect the results of reconstructive infertility operations.[1] The paucity of reports concerning conservative infertility operations in clinic populations is striking.[2] Three conclusions may be drawn: (1) extensive pelvic disease is frequently found in clinic populations and conservative operations are rarely performed; (2) infertility operations are not available to clinic patients; and/or (3) poor surgical results are not reported.

The Endocrinology-Infertility Clinic of the Women's Hospital, Los Angeles County/University of Southern California Medical Center was established in September, 1969. This clinic serves an indigent population, approximately 70 per cent of the patients being of Mexican-American background. Reconstructive infertility surgery was only one of several new services offered to these patients. This paper will review the diagnostic techniques, the criteria used in selecting patients for reconstructive operation, and the results in patients followed at least six months postoperatively.

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Material and methods

Patients are referred to the Endocrinology-Infertility Clinic from other clinics in the Women's Hospital, local public health clinics, and physicians in private practice. Between November 1, 1969, and September 30, 1973, 155 of over 2,000 patients referred to the clinic underwent laparoscopy as part of their infertility evalution.

Following a complete history and physical examination, routine laboratory studies are performed. The infertility evaluation proceeds in a sequential fashion based on the patient's menstrual history (Table I). At least one biopsy is obtained to ensure the absence of an endometrial lesion (e.g., unsuspected pelvic tuber-

Table I. Outline of infertility evaluation

Normal cycles	*Oligomenorrhea-amenorrhea*
1. Postcoital test Semen analysis	1. Endometrial biopsy
2. Serum progesterone Endometrial biopsy	2. Progesterone withdrawal Clomid Serum progesterone Semen analysis
3. Hysterosalpingogram	3. Post-coital test
4. Laparoscopy	4. Hysterosalpingogram
	5. Laparoscopy

culosis) and to ascertain the endometrial response in the luteal phase. Patients with oligomenorrhea or amenorrhea ovulate infrequently or not at all. Because of the association between "chronic" anovulation and endometrial atypia,[3] an endometrial biopsy is indicated in these patients as well. Following the biopsy, the intramuscular progesterone-challenge test is used.[4] If withdrawal bleeding does not occur, significant hypothalamic-pituitary-ovarian disease is suspected, and additional diagnostic studies are performed. If the patient does bleed after progesterone administration, a diagnosis of either polycystic ovarian disease or hypothalamic-pituitary dysfunction is made. In either condition, when infertility is the problem, clomiphene citrate (Clomid*) therapy is utilized. Clomid therapy is continued as outlined by Rust and associates.[5] A serum progesterone concentration of 3 ng. per milliliter or greater, 14 to 19 days after the last Clomid tablet, is presumptive evidence of ovulation.[6]

Once ovulation has been established, further evaluation of both groups proceeds in a similar fashion. The fractional in vivo postcoital test described by Davajan and Kunitake[7] is performed on Day 12 of a spontaneous cycle or five to seven days after the last Clomid tablet. A normal result, five or more motile sperm per high-power field at the level of the internal os, is presumptive evidence that the male factor is adequate. However, for confirmation, a semen analysis is also performed.

Following these studies, and after correction of any abnormalities, the tubal factor is investigated by both hysterosalpingography and laparoscopy. Outpatient hysterosalpingograms are performed without premedication under image intensification fluoroscopy by resident or staff physicians from the Department of Radiology. A Malmström-Westman vacuum cannula is used to instill water-soluble contrast medium into the uterine cavity. The x-rays are reviewed by both the radiologists and the authors.

Laparoscopy is the final diagnostic step in the routine infertility investigation and is performed in the follicular phase of the menstrual cycle with general endotracheal anesthesia and a double-puncture technique. Prior pelvic operation is usually not a deterrent to an adequate laparoscopic examination. Of the 155 patients who underwent uneventful laparoscopy in this study, 38 (25 per cent) had a history of previous pelvic operation, usually salpingectomy for ectopic pregnancy. During laparoscopy, chromopertubation is carried out with a dilute indigo carmine solution instilled via a No. 8 Foley catheter placed in the uterine cavity. The decision to proceed with conservative infertility operation is made at the time of laparoscopy.

Prior to laparoscopy, all possible pelvic findings and surgical risks are explained to the patient. If pelvic pathology is confirmed or unsuspected pathology is found, the patient is prepared to undergo definitive tubal or pelvic operation immediately following laparoscopy with the use of the same anesthetic. A broad-spectrum antibiotic is administered prophylactically during and after laparotomy. All infertility operations are performed by residents under the direction of one of the authors (R. I.)

For those patients with distal tubal obstruction, cuff salpingostomies are performed *without* the use of prosthetic devices. Beginning postoperatively and with continuation of antibiotic coverage for the next six months in the follicular phase of the menstrual cycle, hydrotubations are carried out with saline containing cortisone acetate. For reversal of prior sterilization operations or for correction of segmental tubal obstruction, an end-to-end anastomosis is indicated, during which a tubal splint is utilized *only* during suture placement. In a cornual implantation, a Shirodkar-type prosthesis is used to splint the reimplanted areas. This is removed transcervically five to six months postoperatively with an intrauterine contraceptive device removal hook. If the uterus is not in an anterior position, a modified Gilliam suspension becomes part of the conservative operation. Before the peritoneum is closed, a low–molecular weight dextran solution is left in the pelvis.

Results

Hysterosalpinography (HSG) versus laparoscopy. Of the 155 patients undergoing diagnostic laparoscopy during the study period, 117 (75 per cent) had HSG as well. There was agreement between the two studies in 85 (73 per cent) of the 117 patients. Similar findings have been reported in other series.[3, 9]

*Wm. S. Merrell Co., Div. Richardson-Merrell, Inc., 110 E. Amity Rd., Cincinnati, Ohio 45215.

Discrepancies between HSG and laparoscopy were noted in the other 32 patients (27 per cent). In reviewing the radiographic and laparoscopic findings in these 32 patients, no consistent differences could be found. The HSG was inaccurate in 22 of the 32 cases. In 19, the HSG incorrectly revealed tubal obstruction; 10 of the 19 had tubal fill without spill and the other nine had cornual obstruction, but patency was demonstrated at laparoscopy in all 19 patients. Three other patients had cornual obstruction demonstrated by HSG, but only distal obstruction was found during laparoscopy. HSG has technical problems that laparoscopy can overcome. For example, a unilateral tubal block visualized with HSG occasionally can be overcome at laparoscopy by occluding the patent tube at the uterine cornu with a probe while continuing to instill the dye transcervically. In all likelihood, this phenomenon reflects varying intratubal pressures. During HSG, leakage around the cervical cannula into the vagina may prevent the establishment of adequate intrauterine pressure. Similarly, failure to use a sufficient amount of contrast medium will produce an inadequate study. Tubal spasm caused by temperature differences between the solution and the tissue, rapid dye instillation, or other factors may create the false impression of cornual obstruction. It has been suggested that the discrepancies between HSG and laparoscopy may be explained by differences in the physical and chemical characteristics of the various media used for tubal perfusion.[9] However, in another study performed by the authors,[10] laparoscopy was carried out with simultaneous hysteroscopy with a viscid dextran solution* (molecular weight 70,000) for uterine cavity distention. Free flow of the dextran through the Fallopian tubes was seen. Finally, the effect of anesthetic agents[11] may be an important factor in determining how freely various solutions traverse the Fallopian tubes.

In the remaining 10 cases, the differences noted between HSG and laparoscopy could not be attributed solely to inaccurate radiographic studies. In five of the 10 patients, the HSG demonstrated patency, but laparoscopy revealed distal obstruction. The other five patients had distal obstruction demonstrated by HSG, but cornual obstruction was found at laparoscopy. Since the interval between HSG and laparoscopy ranged between two and six months, these differences could be attributed to advancing disease or a subsequent reaction to the HSG procedure. On occasion, mechanical problems associated with chromopertubation at laparoscopy were encountered.

*Hyskon (30 per cent weight/volume dextran 70 in water), Pharmacia Laboratories, Inc., 800 Centennial Ave., Piscataway, New Jersey 08854.

Table II. Intrauterine abnormalities (No. = 11) found on 117 hysterosalpingograms

Abnormality	*No.*
Intrauterine defects (polyps, submucous myomas, synechiae)	8
Arcuate cavity	1
Salpingitis isthmica nodosa	1
Internal os defect	1

Table III. Findings and subsequent conservative operation in 155 laparoscopies performed because of infertility

Category	*No.*	*%*
Normal pelvis	24	15
Minimal or unilateral disease	19	12
Extensive destruction	28	18
Refused laparotomy	1	1
Laparoscopy only	72	46
Laparoscopy plus conservative operation	83	54
Total	155	100

Table IV. Normal pelvis at laparoscopy

Data	*No.*
Normal pelvis	24 (15%)
Additional infertility factors)	18
Hysterosalpingograms	
Abnormal	7 (29%)
Normal	9
Not done	8
Follow-up (8-45 months)	22
Pregnancies	
Term	6
Abortion	1

HSG remains an important part of the infertility work-up. As seen in Table II, approximately 10 per cent of the patients undergoing both HSG and laparoscopy had an unsuspected intrauterine finding revealed on x-ray. Confirmatory hysteroscopy should be performed in any patient with an intra-uterine defect demonstrated on HSG.

Laparoscopy. As seen in Table III, 72 (46 per cent) of the 155 patients underwent laparoscopy only. All of these patients were discharged 8 to 24 hours postoperatively. There were no intraoperative or postoperative complications.

Table V. Minimal or unilateral disease at laparoscopy

Findings	*No.*
Minimal or unilateral disease	19 (12%)
Additional infertility factor(s)	14
Endometriosis, minimal	4
Unilateral normal + contralateral obliteration	7
Adhesions, minimal	5
Fimbrial "phimosis"	3
Follow-up (8-42 months)	17
Pregnancies	
Term	4
Abortions	2

Table VI. Extensive destruction at laparoscopy

Findings	*No.*
Extensive destruction	28 (18%)
Prior tubal sterilization	3
Extensive adhesions + dilated hydrosalpinges	19
Proximal + distal tubal blocks	6
Pregnancies (after 7-46 months)	0

Normal pelvis. At laparoscopy, 24 patients had no pelvic pathology (Table IV). Eighteen (75 per cent) had one or more additional factors that could explain their infertility. Seven (29 per cent) of these patients had a tubal abnormality demonstrated by HSG which could not be substantiated by diagnostic laparoscopy. Follow-up in these patients ranged from 8 to 45 months with a mean of 22 months. Seven patients (29 per cent) subsequently became pregnant; six pregnancies were carried to term, and one ended in a spontaneous first-trimester abortion. Six of the pregnancies occurred in patients who had additional infertility factor(s) that eventually responded to therapy. Thus, patients who have a completed work-up and a normal pelvis but no other factors diagnosed to explain their infertility have a poorer prognosis regarding pregnancy.

Minimal or unilateral disease. At laparoscopy, 19 patients had minimal or unilateral adnexal disease (Table V). One or more additional infertility factors were present in 14 (74 per cent) of the 19. Follow-up ranged from 8 to 42 months with a mean of 17 months. Six pregnancies have occurred; four patients were delivered at term, one had a spontaneous first-trimester abortion, and one requested termination of pregnancy during the first trimester. Of the seven patients with one normal tube and obliteration of the contralateral side, four had additional infertility factors and have remained infertile; two of the other three conceived. Three of the five patients with minimal adhesions had no other infertility factors, and the adhesions were lysed under laparoscopic control; two subsequently conceived. Therefore, in this group of patients who demonstrated some pelvic abnormalities, the presence of an additional infertility factor seemed to have an adverse effect upon prognosis.

Table VII. Results of conservative operation

Operation	*Pregnancies*						
		Total					*Patency rate*
Type	*No.*	*No.*	*%*	*T*	*E*	*AB*	*(%)*
Salpingostomy	27	10(7)	26	2	6	2	60
End-to-end anastomosis	6	2	33	1	0	1	80
Implantation	8	2(1)	13	2	0	0	33
Salpingolysis	18	3	17	3	0	0	90
Myomectomy	9	1	11	1	0	0	–
Estes procedure	1	0	–	0	0	0	–
Combined procedure	14	1	7	0	1	0	60
Total	83	19(15)	18	9	7	3	

T = term; E = ectopic; AB = abortion.

Extensive destruction. Table VI outlines a group of 28 patients in whom reconstructive operation seemed unwarranted because of extensive tubal destruction. The mean age was 27 years. Seventeen patients (61 per cent) were less than 30 years old, and two were only 19. Three patients had prior tubal sterilizations, two of these being laparoscopic fulgurations. All hysterosalpingograms revealed proximal or distal blocks without intraperitoneal spill of the contrast material. No tubal patency was detected at laparoscopy. The 19 patients with extensive adhesions and bilateral hydrosalpinges had tubal dilatation extending to the cornual portion of the uterus with pale, thin-walled tubes. No patient became pregnant over the 7 to 46 month (mean 19 months) follow-up period.

Laparoscopy plus conservative operation. The final category consisted of 83 (54 per cent) of the 155 patients. In this group, diagnostic laparoscopy was followed by conservative pelvic operation. Forty-four (53 per cent) of the 83 patients had one or more additional infertility factors. Prior to operation, these factors had responded to therapy. Anovulation was the primary additional factor, but abnormal semen analyses and "poor" cervical mucus were also encountered. Another 27 (32.5 per cent) patients had undergone prior pelvic operations. Salpingectomy,

tubal sterilization, and ovarian cystectomy were the most common procedures.

The types of surgical procedures, pregnancies, and patency rates are outlined in Table VII. The classification is based upon the *major* procedure performed. However, lysis of adhesions was performed with all the salpingostomies and combined procedures and with most of the myomectomies. No intraoperative or postoperative complications occurred.

Follow-up in the 27 patients undergoing cuff salpingostomy ranged between 5 and 34 months (mean 15 months). Twenty patients returned for postoperative HSG; 12 (60 per cent) had tubal patency. Ten pregnancies occurred in seven patients (26 per cent). However, only two were delivered at term, while six tubal ectopic pregnancies and two spontaneous abortions occurred. In fact, two patients had two tubal pregnancies each. The ectopic pregnancy rate in the patients who had salpingostomy performed was 60 per cent.

Six patients had an end-to-end anastomosis. Over the 5 to 32 month period (mean 10 months) of follow-up, only one term gestation and one spontaneous abortion occurred. The patency rate by HSG was 80 per cent.

One of the eight patients undergoing cornual implantation became pregnant twice. Both pregnancies were uneventful. She was delivered by cesarean section at term, and both cornual areas were quite thin with dilated veins. HSG performed 12 weeks after the first cesarean section revealed an intact uterine cavity without cornual defects. A bilateral salpingectomy for sterilization was performed at the time of repeat cesarean section. The patency rate in the cornual implantation group was 33 per cent. The period of follow-up was 7 to 25 months (mean 13 months).

Among 18 patients who had salpingolysis performed, only three term pregnancies occurred. The period of follow-up was 6 to 46 months (mean 24 months). The patency rate was 90 per cent. The low pregnancy rate might be attributed to the fact that 16 (89 per cent) of the 18 patients had additional infertility factor(s). Additionally, at operation, 11 (61 per cent) had associated pelvic pathology, such as extensive unilateral adnexal disease necessitating salpingo-oophorectomy or marked salpingitis isthmica nodosa.

Seven (78 per cent) of the nine patients undergoing myomectomy had one or more additional infertility factors. The period of follow-up was between 6 and 26 months (mean 13 months), and only one patient became pregnant.

Fourteen patients underwent combined operative procedures. The most frequent type was myomectomy and tuboplasty, but combined linear and cuff salpingostomies are included as well. The postoperative patency rate was 60 per cent. Over the 6 to 46 month (mean 25 months) period of follow-up, only one pregnancy occurred, and this was an ectopic gestation.

Comment

The importance of diagnostic laparoscopy as an integral part of a proper infertility work-up has been stressed previously.[12, 13] For accurate tubal evaluation and over-all pelvic assessment, laparoscopy is superior to HSG. If the hysterosalpingogram is obtained as the "final" study in the infertility work-up or only for its "therapeutic" benefit, then its continuing value must be questioned. However, as an adjuvant study to the laparoscopist and infertility surgeon, HSG can be of significant benefit. In the operating room, a hysterosalpingogram should be present for comparison with the laparoscopic findings. Occasionally, mechanical problems will preclude transuterine dye instillation at laparoscopy, and HSG will provide the only evidence of tubal fill and/or spill. If a history of pelvic inflammatory disease is given by the patient, HSG can provide helpful, prognostic information[14] for the physician-patient discussion as it relates to the proposed operation. The reality of a cornual block seen at laparoscopy is made more convincing if the same finding was noted by earlier HSG. Only a patient with a bilateral cornual block which has been definitively proved should be subjected to a reimplantation operation. Finally, as seen in Table II, approximately 10 per cent of the patients undergoing HSG had an unsuspected intrauterine finding revealed. The availability of hysteroscopy permits these intrauterine defects to be identified definitively. Hysteroscopy can be performed with local anesthesia in a clinic or office setting. It can also be carried out in conjunction with laparoscopy as the final diagnostic step in the routine infertility work-up.

In addition to its value in diagnosing unsuspected pelvic pathology, laparoscopy is an essential primary step when conservative infertility operation is contemplated. The laparoscope can reveal a normal pelvis, thus eliminating the need for further operation. With the laparoscope, the infertility surgeon can begin to define and categorize the degree of pelvic disease and distortion. In some instances, operation can be deferred, and the medical work-up and/or therapy can be continued on a more solid basis when an accurate laparoscopic view of the pelvis is obtained. In other cases, laparoscopy can reveal such extensive pelvic destruction that laparotomy is avoided and the patient can be advised to abandon further infertility studies

and consider adoption. In view of its importance in determining the degree of pelvic pathology and the necessity for conservative infertility operation, laparoscopy in the infertile patient should be carried out *only* by a gynecologic surgeon who is prepared to make endoscopic judgments and perform the required operation.

The importance of a thorough infertility evaluation prior to laparoscopy cannot be overemphasized. If no explanation for the infertility is found, laparoscopy then becomes an essential diagnostic step. If an infertility factor such as anovulation or poor cervical mucus is discovered, it should be corrected and treated for at least six months before the patient is subjected to surgical investigation. In our study, the presence or absence of additional infertility factors played a prognostic role when combined with the laparoscopic findings. When the laparoscope revealed a normal pelvis, the presence of an infertility factor that had responded to treatment was an encouraging sign. Of the seven pregnancies, six occurred in patients who had a diagnosed infertility factor which was being treated at the time of laparoscopy. On the other hand, the patient who has minimal or unilateral disease at laparoscopy has a more favorable outlook for pregnancy *if* the pelvic pathology is not compounded by an additional infertility factor. Furthermore, the laparoscope can be an operative instrument in the presence of minimal pathology, or it permits an "educated delay" in the infertility operation with the possibility that a pregnancy may ensue.

In this study, when conservative infertility operation followed laparoscopy in 83 (54 per cent) of the 155 patients, only 19 pregnancies occurred in 15 patients. Many factors contributed to this relatively low success rate. Forty-four (53 per cent) of the 83 patients had one or more additional infertility factors which were being treated when conservative operation was performed. With the exception of the salpingolysis category, no pregnancies have occurred in this group. Thus, extensive tubal operation seems contraindicated in the presence of additional infertility factor(s). Another 27 patients (32.5 per cent) had undergone prior pelvic operation. Although difficult to implicate as a specific etiologic factor, a surgical history of unilateral salpingectomy or ovarian cystectomy may play an additive role in the over-all infertility picture. With the exception of the end-to-end anastomoses and the cornual implantations, the vast majority of surgical procedures were performed in the presence of significant tubal damage and associated pelvic adhesions.

The explanation for the disturbing results in the 27 salpingostomy cases may be found in the surgical findings. Dilated Fallopian tubes lacking an intact endosalpinx and surrounded by varying degrees of pelvic adhesions will respond to the surgeon's knife, but the latter cannot repair intrinsic anatomic and physiologic tubal damage. Superficially, a 26 per cent pregnancy rate coupled with a 60 per cent tubal patency rate may seem acceptable. As suggested by Umezaki and associates[15] salpingostomy-treated tubes may require a longer healing time, so our results could improve with continued follow-up. However, of the 10 pregnancies, only two have culminated in term gestations, and six tubal ectopic pregnancies have occurred. Since 60 per cent of the pregnancies in patients who had salpingostomy resulted in tubal implantations, the risk-benefit ratio of this type of tubal operation must be seriously considered. Although the significant amount of pelvic disease found in this clinic population may explain the high tubal-to-intrauterine gestation ratio, Swolin,[16] despite meticulously performed operation with the use of microdissection techniques, has reported comparable findings from a Scandinavian population exhibiting less extensive pelvic pathology.

Although only 83 (54 per cent) of the 155 infertility patients in this series underwent conservative operation following diagnostic laparoscopy, the poor results in this group—nine term gestations, seven tubal ectopic pregnancies, and three abortions—indicate the need for even greater endoscopic selectivity. Unless the laparoscope is utilized even more critically, especially in those patients with additional infertility factor(s), the low term pregnancy rate and the high number of ectopic pregnancies do not justify conservative infertility operation in a population prone to chronic pelvic inflammatory disease.

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Estrogen potencies of three new low-dose oral contraceptives

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The estrogen potencies of three new oral contraceptive formulations—Brevicon, Modicon, and Lo/Ovral—were determined. Brevicon and Modicon were found to have estrogen potency equal to mestranol 50 μg and equal to or greater than Norinyl 1 + 50 and Ortho-Novum 1 + 50. Lo/Ovral, which is identical to Ovral in the type and ratio of progestin but 40 per cent lower in drug content, could be estimated to have an estrogen potency of 0.73 relative to mestranol 50 μg and therefore, by inference, to Brevicon and Modicon.

THE ESTROGEN potency of oral contraceptives marketed in the United States has recently been reported.[1] Since then, two new oral contraceptive formulations with estrogen content less than 50 μg have been introduced. These are: ethinyl estradiol 35 μg combined with norethindrone 0.5 mg., marketed under the names Brevicon* and Modicon,† and ethinyl estradiol 30 μg combined with norgestrel 0.3 mg., marketed under the name Lo/Ovral.‡ Since the estrogen potency of oral contraceptives is dependent on the type and dose of the progestin as well as the estrogen component of the pill, oral contraceptives with descreased amounts of estrogen may not necessarily have decreased estrogen potency.[1] The progestins norethindrone, norethindrone acetate, and ethynodiol diacetate exhibit both estrogenic[2] and antiestrogenic[3] activity in animal assays. These progestins when present in oral contraceptives in ratios of progestin to estrogen of 20:1 to 50:1 potentiate estrogen potency at low doses and inhibit estrogen potency at high doses.[1] Norgestrel exhibits only antiestrogen activity and in a ratio of 10:1 inhibits estrogen potency at all doses.[1] The type of estrogen used also influences estrogen potency. In a previous study, mestranol had only 67 per cent the estrogen potency of ethinyl estradiol.[1]

Since Lo/Ovral contains the same estrogen and progestin in identical proportions as Ovral,* the estrogen potency can be calculated from previously determined data.[1] Modicon and Brevicon are different from other oral contraceptives which utilize norethindrone as a progestin in both the type of estrogen (ethinyl estradiol, rather than mestranol) and the ratio of progestin to estrogen. It is therefore necessary to perform further dose-response assays in order to compare the estrogen potency of these compounds with those of the oral contraceptives studied previously. In addition, the estrogen potency of an experimental contraceptive combination containing ethinyl estradiol 35 μg and norethindrone 1.0 mg. was assayed in order to learn more about the effect of altering the ratio of progestin to estrogen.

Materials and methods

Samples of Brevicon, Norinyl 1 + 50,† ethinyl estradiol 35 μg, and mestranol 50 μg were obtained from commercial sources. In addition, an experimental contraceptive formulation containing ethinyl estradiol

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Table I. Comparison of potency by analysis of variance

Compound	*No.*	*Regression coefficient +S.E.E.**	*Relative potency (95 per cent confidence limits)*
Group I—Regression lines parallel to ethinyl estradiol:			
Ethinyl estradiol 35 μg	61	22.26 ± 0.75	1.00
Mestranol 50 μg	75	20.34 ± 1.71	1.02 (0.64 – 2.05)
Brevicon	38	24.53 ± 3.63	1.05 (0.75 – 1.30)
Group II—Regression lines parallel to norinyl 1 + 50:			
Norinyl 1 + 50	86	12.50 ± 0.16	1.00
Ethinyl estradiol 35 μg + Norethindrone 1.0	36	12.41 ± 0.91	1.18 (0.5 – 2.11)

*Standard error of the estimate.

35 μg combined with norethindrone 1.0 μg was compounded by adding 0.5 mg. of norethindrone to Brevicon. The study was conducted as described previously.[1] All compounds were suspended in vehicle and given orally for 3 days to 21 day-old-female Swiss Webster mice. The increase in uterine weight was utilized as an index of estrogen potency and results were expressed as wet uterine weight per 100 Gm. of body weight. The assay was performed twice with an interval of 3 weeks. The relative potency of drugs with similar regression coefficients was calculated by the parallel-line analysis of variance of Finney.[4] The relative potency of drugs with nonparallel regression line was determined by comparing the effects of identical doses. A previous study showed that when comparing estrogen potency of compounds with non parallel dose response lines, the classical method of determining the dose required to double or triple uterine weight was not satisfactory. A determination of the increase in uterine weight produced by identical doses of different drugs gave the best responses over a wide range of doses.[1]

Results

The regression coefficients (slopes) and standard error of the estimate for the linear portion of the log dose-response curve are shown in Table I. Comparison of the regression lines of mestranol 50 μg and Norinyl 1 + 50 with results obtained in the earlier study shows homogeneity of regression. There was no significant difference in slope despite the decrease in the amount of response. In addition, comparison of uterine weights for mestranol 50 μg and Norinyl 1 + 50 in the two studies shows no significant differences within the limits of the bioassay.

The regression coefficient of Brevicon (24.53) was identical to that of ethinyl estradiol 35 μg (22.26) and mestranol 50 μg (20.34). Also the estrogen potency of Brevicon calculated by analysis of variance was identical to that of ethinyl estradiol 35 μg and mestranol 50 μg. The regression coefficient of ethinyl estradiol 35 μg combined with norethindrone 1.0 mg. (12.41) was identical to that of Norinyl 1 + 50 (12.50). Both of these regression coefficients were markedly different from those of Brevicon, ethinyl estradiol, and mestranol. The estrogen potency of ethinyl estradiol 35 μg plus norethindrone 1.0 was not significantly greater than that of Norinyl 1 + 50.

Lo/Ovral‡ has the same type and ratio but only 60 per cent of the amount of progestin and estrogen as Ovral,‡ which contains ethinyl estradiol 50 μg combined with norgestrel 0.5 mg. Since the linear regression coefficient of Ovral (24.9) and its potency (0.819) relative to ethinyl estradiol 50 μg (100) are already known, Lo/Ovral can be calculated to have a potency of 0.486 relative to ethinyl estradiol 50 μg or of 0.729 relative to mestranol 50 μg.

Relative estrogen potency as determined by the effect on uterine weight of identical fractional doses is shown in Table II. The equivalent estradiol dose is the fractional dose of ethinyl estradiol which could produce the same uterine weight effect as the indicated fractional dose of the pill. The three fractional doses used for this comparison are those which produced 25 per cent, 50 per cent, and 75 per cent of the maximum increase in uterine weight in a previous study when ethinyl estradiol 50 μg was administered. In the present study, only ethinyl estradiol 35 μg was assayed; however, relative estrogen potency is expressed in terms of both ethinyl estradiol 50 μg and ethinyl estradiol 35 μg. It can be seen that at 0.00155, the dose which produced 25 per cent of the maximum response, the estrogen potencies of Brevicon and Norinyl 1 + 50 were identical. In contrast, at higher fractional doses, Brevicon was decidedly more estrogenic than Norinyl 1 + 50. At 0.00155, Brevicon and Norinyl 1 + 50 had potencies of 1.06 and 1.08, respectively, relative to ethinyl estradiol 50 μg.

The effect of altering the ratio of progestin to estrogen is very apparent when Brevicon is compared

Table II. Relative potency: Uterine effect produced by identical fractional dose

Compound	Fractional dose: 0.00155 — Uterine wt. / Body wt.	Estradiol 50 μg equiv.	Potency relative to E. estradiol: 35 μg	50 μg	Fractional dose: 0.0032 — Uterine wt. / Body wt.	Estradiol 50 μg equiv.	Potency relative to E. estradiol: 35 μg	50 μg
Ethinyl estradiol (35 μg)	8.7	0.00155	1.00	0.70	15.6	0.0032	1.00	0.70
Mestranol (50 μg)	10.9	0.00190	1.23	0.86	16.4	0.0035	1.05	0.72
Brevicon	12.4	0.00235	1.52	1.06	18.4	0.043	1.34	0.94
Norinyl 1 + 50	12.5	0.00240	1.55	1.08	16.8	0.00365	1.07	0.80
Ethinyl estradiol 35 μg + norethindrone 1.0 mg.	15.6	0.00320	2.06	1.42	19.3	0.0047	1.47	1.01

to ethinyl estradiol 35 μg plus norethindrone 1.0 mg. At the lowest fractional dosage of ethinyl estradiol 35 μg plus norethindrone 1.0 mg. only the additive or estrogenic effect of the progestin occurs. Therefore, this compound is more estrogenic than Brevicon at this dosage. The estrogen potency derived from ethinyl estradiol 35 μg alone was 0.70 in each case, whereas that derived from norethindrone 0.5 mg. was 1.06 − 0.70 or 0.36 (34 per cent) of the total and for norethindrone 1.0 was 1.42 − 0.70 or 0.72 (51 per cent) of the total. At the middle fractional dose this situation is changed so that the apparent estrogen potency contributed by norethindrone 0.5 is only 0.24 and that contributed by norethindrone 1.0 is only 0.31. At the highest of the three fractional doses the apparent contribution by norethindrone 0.5 is only 0.14 and the contribution by norethindrone 1.0 is only 0.05. In the case of Norinyl 1 + 50 which contains the weaker estrogen, mestranol, the estrogen contribution by norethindrone 1.0 is 1.08 − 0.86 or 0.22 at the lowest fractional dose and is already less than the 0.72 of ethinyl estradiol 35 μg + norethindrone 1.0 mg. at this dose. At the highest dose the antiestrogenic nature of this effect is apparent when the estrogen potency of the total pill is less than that of mestranol 50 μg alone.

Comment

The estrogen potency of Brevicon and Modicon which contain ethinyl estradiol 35 μg and norethindrone 0.5 mg. is shown in the present study to be equal to or greater than the estrogen potency of Norinyl 1 + 50 and Ortho-Novum 1 + 50 which contain mestranol 50 μg and norethindrone 1.0 mg. At a fractional dose of 0.00155 the estrogen potency of Modicon and Brevicon was 1.06 and of Norinyl 1 + 50 or Ortho-Novum 1 + 50 was 1.08 relative to ethinyl estradiol 50 μg = 1.00. The principal cause for the equal estrogen potency of these compounds, despite their differences in amount of estrogen content, is that ethinyl estradiol has a greater estrogen potency than mestranol.

The contribution of norethindrone to the estrogen potency of oral contraceptives appears to be more important than previously thought.[2] Two different doses of norethindrone combined with ethinyl estradiol 35 μg were studied. At low doses of the total pill the amounts of estrogen potency contributed by norethindrone 0.5 mg. and 1.0 mg. were equal to 52 per cent and 106 per cent, respectively, of that contributed by ethinyl estradiol 35 μg. Thus, norethindrone had 3.6 per cent of the estrogen activity of an equal amount of ethinyl estradiol in the present study. At higher doses of the total pill, norethindrone acts as an antagonist to ethinyl estradiol so that its estrogen effect is negated. A similar effect had been noted previously for norethindrone acetate.[1] The contribution to total estrogen potency of norethindrone 1.0 mg. was only half as great when combined with mestranol 50 μg as when combined with ethinyl estradiol 35 μg. Further studies are needed to explain this difference.

The estrogen potency of Lo/Ovral, another new low estrogen oral contraceptive pill containing ethinyl estradiol 0.30 mg., was calculated without additional assays, since it contains the same type and ratio of estrogen and progestin as Ovral, which had been studied previously.[1] The estrogen potency of Lo/Ovral was calculated to be 0.49 relative to ethinyl estradiol 50 μg and 0.73 relative to mestranol 50 μg. Of the three pills studied only Lo/Ovral therefore appears to offer a significant reduction in estrogen potency compared to oral contraceptives containing 50 μg of estrogen.

Although the use of bioassay in animals to determine estrogen potency of drugs is well established, the relationship of such potency to the effect of estrogen in human subjects is not known. Several possibilities for disparity exist. The manner of absorption, metabolism,

0.0067			
Uterine wt. / Body wt.	*Estradiol 50 μg equiv.*	*Potency relative to E. estradiol*	
		35 μg	*50 μg*
22.5	0.0067	1.00	0.70
22.5	0.0067	1.00	0.70
24.7	0.0081	1.20	0.84
21.2	0.0058	0.87	0.62
23.5	0.0072	1.08	0.75

excretion, or tissue receptor interaction may differ between species. More important to the clinical use of information obtained by bioassay is the probability that a growth effect on Müllerian duct derivatives is only one of many actions of estrogen in the humans. Estrogen effect on fluid retention and estrogen effects on numerous serum components including those involved in blood clotting are other well-known actions. These non-Müllerian actions may not be subject to the same laws which govern estrogen potency in the reproductive system. A correlation between the relative estrogen potency determined by bioassay and the incidence of thromboembolic events had previously been suggested and was attributed to the antiestrogen effect of certain progestins.[1] A recent report of a prospective study of pill users in Great Britain confirms that the incidence of vein thrombosis decreases as the ratio of progestin to estrogen is increased.[5] Further studies are needed to confirm this observation and to find out if it can be extended to other effects of estrogen in women. The clinician should be aware of the possible disparities between animal and human effects before attempting to apply estrogen potency data obtained by bioassay to clinical usage. Until equivalent studies of estrogen potency in man are available, however, animals studies such as the present demand consideration by clinicians as well as research pharmacologists.

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Measured intelligence in offspring of oral and nonoral contraceptive users

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A study has been made of measures of intelligence of 210 children (5 to 8 years of age) born to mothers who used oral and nonoral contraceptives pregestationally. Ninety-six of these children were born to mothers who used oral contraceptives, and one hundred and fourteen were born to mothers who used vaginal contraceptive methods. The intelligence of the children was measured in the form of the full-scale I.Q. score by the Wechsler Intelligence Scale for Children (WISC) adapted and normalized for Puerto Rico by the Puerto Rico Department of Education. A three-factor analysis of variance was performed on the data collected for comparison of the two groups. It was observed that there was no significant difference between the average I.Q. scores of children born to mothers using oral contraceptives and those born to the mothers using nonoral contraceptives. The average I.Q. in children of the oral contraceptive group was 85.04 and that in children of the nonoral contraceptive group was 85.54. Distributions for both groups were also found to be similar. No significant differences between means were observed for sex, age, and interactions with the exception of the age and sex interaction, where, again, no specific, meaningful trend could be established. The average I.Q. in the sample fell very close to the center of the "normal" range of the WISC, Puerto Rican adaptation. The results of the study do not offer any evidence as to the effect of the use of oral contraceptives on the intelligence measure (by the WISC) of the offspring born to mothers using them pregestationally. The children under study, on an average, are of "normal" intelligence as measured by the Puerto Rican intelligence standards.

THE ORAL CONTRACEPTIVE, commonly known as "the pill," has been employed more and more as a method of family planning. As its use increases, different segments of society are asking themselves about its possible effects on women and their offspring.

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Some of the effects on mothers and fetuses have been mentioned in previous studies.[3-8] Numerous articles in the lay press also have focused attention on the alleged harmful effects of the contraceptive pill. Some have claimed congenital and physical defects and low intelligence quotients in the offspring of mothers who have received antenatal norethynodrel.[1, 2] However, one of the specific questions remaining unanswered was whether the administration of oral contraceptive steroids immediately prior to pregnancy had any relationship to the intelligence of the child. A review of the available literature, up to 1971, indicated that this subject, although mentioned in a few articles, had not been formally investigated.

This made evident the need for research directed toward identifying and understanding in a more scientific way the effects of oral contraceptives on the intelligence of children born to mothers who used them. The present report reveals some important

findings of a controlled experiment being carried out in the Maternal Health Program at the University of Puerto Rico Medical School.

Method

The subjects for the study were obtained from the Maternal Health Study Program which was designed in 1961 to study the incidence of genital and breast cancer in women who were taking progestational agents. Subjects admitted to the study program met basic minimum qualifications such as: age 21 to 39 years old, at least one normal pregnancy, and no prior use of oral contraceptives or intrauterine contraceptive devices. Each candidate, before admission to the program agreed to use the contraceptive to be prescribed.

Once a woman was found eligible, and prior to the physical examination, she was assigned at random to the experimental (oral contraceptive) or the control (nonoral contraceptive) group* which she was to follow throughout the experiment.

The 5,465 subjects of the present study were admitted to one of the clinics in the project between 1961 and 1969. The randomization procedure assigned 2,741 women (50.16 percent) to the study group (oral contraceptive) and 2,724 (49.84 per cent) to the control group (nonoral contraceptive). A comparison of several socioeconomic characteristics of the randomly selected subjects for our two groups such as age, education, family income, occupation, etc., showed that both groups (oral and nonoral contraceptive) were identical and, therefore, comparable.[6]

The next step was to identify the mothers who had offspring after admission to the study. These were mostly voluntary pregnancies, since there were no cases of contraception failure among the oral group. During the period 1961 to 1969, 398 children were born to the 5,465 women. Of the 398 children, 229 (57.54 per cent) were between ages 5 and 8 at the time of the study, an age range suitable for the psychological tests to be used. Of these 229 children, 210 were included in the study. The other nineteen patients (11 users of oral contraceptives and 8 users of nonoral contraceptives) were excluded either because the children were dead or because they had moved out to other communities and therefore were lost to study.

The subjects of the study were distributed as follows: 96 children (41 boys and 55 girls) were in the group whose mothers used oral contraceptives, and 114 (60 boys and 54 girls) were in that of the women who used nonoral contraceptives. The average ages of the two groups were 6.1 years for the study group (oral contraceptives) and 6.2 years for the control group (nonoral contraceptives).

*The oral contraceptive group used norethynodrel, 5 mg., and mestranol, 0.075 mg. (Enovid, G. D. Searle & Co.). The total steroid dosage was 5.75 mg. per tablet. The control group used vaginal methods such as diaphragms, prophylactics, suppositories, etc.

Table I. Analysis of variance of the full-scale I.Q. scores

Source of variance	*Degrees of freedom*	*Mean square*	*F ratio*
Contraceptive treatment (C)	1	11.05	0.07
Sex (S)	1	237.86	1.58
Age (A)	2	153.21	1.02
C-S interaction	1	183.09	1.22
C-A interaction	2	36.71	0.24
S-A interaction	2	655.55	4.37*
C-S-A interaction	2	407.77	2.72
Error	198	150.19	
Total	209	156.35	

*Significant at 5 per cent level.

Each child was referred at random to one of the two psychologists* who administered a full-scale intelligence test. The test used in the study was the Wechsler Intelligence Scale for Children (WISC) (Escala de Inteligencia Wechsler para Niños) which is translated and adapted for Puerto Rico by the Department of Education of the Commonwealth of Puerto Rico.[9] This test is not a literal translation of the English WISC. It has been adapted after several experimental studies, in 1951, which suggested revisions appropriate to the Puerto Rican language and cultural environment. The test was normalized by Dr. Pablo Roca, then Director of the Evaluation Office of the Department of Education, in consultation with the author of the test, David Wechsler, and the Psychological Corporation of New York. In administering the test, the psychologists followed the manual prepared by David Wechsler for the test in Spanish.[10]

For the purpose of the study, a three-factor (treatment group × sex × age) analysis of variance was performed on the full-scale Intelligence Quotient (I.Q.) scores.

Findings

The analysis of the data revealed that the 96 children of the oral contraceptive group had an average I.Q. score of 85.08 (with a standard deviation of 13.66),

*The psychologists were both Puerto Rican and had their M.A.'s in psychology from recognized United States universities; they were experienced and trained to administer psychological tests.

Table II. Means and standard deviations (S.D.) of WISC (Puerto Rico) I.Q. scores for children of oral and nonoral contraceptive groups by sex and age

Age of children (years)	*Treatment group*				*Both groups*		*Both groups and sex*
	Oral contraceptive		*Nonoral contraceptive*				
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*	
5							
No.	9	12	11	6	20	18	38
Mean	81.44	85.33	82.91	84.50	82.25	85.06	83.58
S.D.	9.42	19.24	10.11	6.24	9.83	16.13	13.27
6							
No.	18	26	28	34	46	60	106
Mean	88.50	83.69	87.75	86.53	88.04	85.30	86.49
S.D.	11.63	11.82	10.85	11.07	11.17	11.49	11.43
7-8							
No.	14	17	21	14	35	31	66
Mean	76.00	92.82	83.24	84.71	80.34	89.16	84.48
S.D.	9.29	12.93	9.60	16.08	10.12	14.99	13.39
All ages							
No.	41	55	60	54	101	109	
Mean	82.68	86.87	85.28	85.83	84.23	86.36	
S.D.	11.78	14.66	10.55	12.22	11.14	13.51	
Both sexes and all ages							
No.	96		114				210
Mean	85.08		85.54				85.33
S.D.	13.66		11.37				12.47

while the 114 children of the nonoral contraceptive group had an average I.Q. score of 85.54 (with a standard deviation of 11.37). The difference (0.48) between the two averages is not statistically significant, as indicated by the F test in the analysis of variance (Table I). It may be noted that the I.Q. score in children of the "oral contraceptive" group ranged from a low score of 55 to a high of 133, while in the nonoral group it ranged from 54 to 118. The I.Q. scores for both groups were similar and essentially distributed normally. Thus, these data suggest that children of both groups (oral and nonoral contraceptive) were almost equal in I.Q. When the groups are combined, the average I.Q. of the 210 children was found to be 85.33 (standard deviation 12.47). This average score compares fairly well with the average I.Q. score of the children in Puerto Rico which is 88, according to a study made by the Department of Education, wherein it is established that the average I.Q. (88) of children in Puerto Rico is equivalent to the average I.Q. (100) by the United States standards.[9]

The results of the F test indicated that none of the main effects (treatment, sex, and age) were significant. Also among the interactions, only the sex and age interaction was found to be significant at the 5 per cent level.

However, when the average I.Q. scores between boys and girls within the age groups were compared, as indicated in Table II, no meanings could be assigned to these differences, as no specific trend could be noticed among the six means. For example, at age 5, the boys had an average I.Q. score 2.81 points lower than girls (82.25 versus 85.06); on the other hand, at the age of 6 (a year-older group), the boys had an average score 2.74 higher than the girls but, once again, the average of boys in the 7- to 8-year-old group was lower by 8.82 points than that of the girls in that group. Thus, even though the age-sex interaction averages show significant differences, no meaningful trend by age or by sex could be established.

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The effects of norgestrel on carbohydrate and lipid metabolism over one year

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Carbohydrate and lipid metabolism were studied with the use of a three-hour oral glucose tolerance test in 71 women before and after one year of daily oral norgestrel, 0.075 mg., treatment. There was no significant change in weight or fasting plasma triglyceride and cholesterol levels. There was a significant elevation of both the blood glucose and plasma insulin levels after one year of treatment. This was true for both the fasting and the glucose-stimulated values. Whereas all of the individual glucose tolerance curves at the pretreatment control test were normal by selection, 15.5 per cent of the curves were borderline abnormal to abnormal at the one-year test. The significance of these metabolic alterations is discussed.

SYNTHETIC OVARIAN steroids are one of the principal family-planning methods used today. During the past two decades, there have been modifications made in steroid contraceptives designed to maintain or improve their effectiveness in pregnancy prevention and to reduce their side effects. In order to progress with this development, a knowledge of the dose-response relationships and steroid-specific relationships had to be gained for each adverse secondary effect. The purpose of this paper is to further that knowledge by reporting the effects of one progestogen, norgestrel, on both carbohydrate and lipid metabolic parameters over one year's duration of treatment.

Methods

The methods used have been published previously and will only be reviewed briefly.[1] Women volunteers were selected from a family-planning clinic, and they were all informed about the research and signed a consent to participate. Many were postpartum (greater than six weeks), and the others had not used steroid contraceptives for three or more months. The women were instructed to ingest a high-carbohydrate diet for three days before the testing and then to report to the metabolic laboratory at 08.00 on the day of the test after having fasted overnight. During the test, they remained seated. An antecubital venous blood sample was drawn, and they were given a solution containing 100 Gm. of glucose to ingest in two minutes. Repeat venous blood samples were drawn at 30, 60, 120, and 180 minutes. The blood was mixed with preservatives, separated, and later analyzed in duplicate for the content of glucose, insulin, triglycerides, and cholesterol.[1]

Following the test, the values for the glucose tolerance test were analyzed, and only women with a normal control curve were selected. These 71 "normal" women were instructed to ingest the steroid contraceptive daily. They were then given norgestrel* and seen regularly by family-planning personnel to resupply the drug, answer questions, and maintain compliance with the method. After one year's treatment, the women were brought back to the laboratory for an identical repeat metabolic test.

Since all of the subjects had a control and one-year test, we are dealing with matched-pair data. All of the

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*The 19-norprogestogen norgestrel, 0.075 mg. tablets were supplied by Wyeth Lab.

Table I. Statistical studies of blood glucose in milligrams per 100 ml. for women having an oral glucose tolerance test before and after one year of treatment with 0.075 mg. norgestrel per day (No. = 71)

Time in hours	*Test*									
	Control					*One year*				
	Fasting	*0.5*	*1*	*2*	*3*	*Fasting*	*0.5*	*1*	*2*	*3*
Mean	77.8	105.5	93.7	82.2	72.7	83.2	124.0	107.2	89.1	77.0
S.E.M.	0.9	2.7	2.7	1.9	2.0	1.1	3.7	3.5	2.8	2.5
Mean difference	5.3	18.6	13.5	6.6	4.7					
t	4.2212	4.7329	3.4023	2.4767	1.7669					
P	<0.001	<0.001	<0.01	<0.05	<N.S.*					

*Not significant.

Table II. Statistical studies of plasma insulin in microunits per milliliter for women having an oral glucose tolerance test before and after one year of treatment with 0.075 mg. of norgestrel per day (No. = 71)

Time in hours	*Test*									
	Control					*One year*				
	Fasting	*0.5*	*1*	*2*	*3*	*Fasting*	*0.5*	*1*	*2*	*3*
Mean	12.6	128.4	113.9	95.2	56.4	17.3	159.4	167.2	132.2	91.2
S.E.M.	0.9	10.2	8.9	7.2	5.0	2.0	10.4	12.2	10.1	8.3
Mean difference	4.7	32.2	51.9	35.8	34.0					
t	2.7199	3.1559	4.4898	3.7672	4.4311					
P	<0.01	<0.01	<0.001	<0.001	<0.001					

laboratory and clinical results were placed on punch cards and appropriately analyzed with the help of a computer for the means, standard deviations, standard errors, differences, means of the differences, and Student's t values. The probability values were taken from two-tail tables, and only values of 0.05 or less were considered significant.

The characteristics of the study group were typical for a family-planning clinic. The mean age was 21.1 ± 0.6 (S.E.M.) years, and the mean parity was 1.9 ± 0.1 (S.E.M.). The mean control weight for the group was 136.6 ± 3.2 (S.E.M.) pounds, and after one year the mean weight was 140.3 ± 3.7 (S.E.M.) pounds. This change was not significant (t = 1.1372; p not significant).

Results

Glucose. The statistical studies of the blood glucose values were shown in Table I. It can be seen that there is a significant elevation in all but the three-hour values at the one-year test. The Wilkerson point score system was utilized to interpret the individual tolerance curves.[1] All of the control curves were normal by population selection. At the one-year test, there were 9 (12.7 per cent) curves that were borderline abnormal and 2 (2.8 per cent) curves that were abnormal. Thus, 11 (15.5 per cent) of the curves deteriorated during the year.

Insulin. The statistical studies of the plasma insulin values are given in Table II. It can be easily seen that there is a significant rise in all of the values at the one-year test.

Triglyceride. The mean fasting plasma triglyceride level for the control test was 78.6 ± 6.0 (S.E.M.) and for the one-year test it was 69.6 ± 5.6 (S.E.M.) mg. per 100 ml. This change is not significant (mean difference, −9.0; t = 1.4601).

Cholesterol. The mean fasting plasma cholesterol for the control test was 130.5 ± 12.3 (S.E.M.) and for the one-year test it was 133.3 ± 7.2 (S.E.M.) mg. per 100 ml. This difference also was not statistically significant (mean difference 2.8; t = 0.2686).

Comment

There are several million women currently using steroid contraceptives. A developmental program has been underway in which an attempt to improve formulation by altering steroid combinations and dosages is being made. In order to do this adequately, a detailed understanding of the metabolic effects of each

component steroid is necessary. The present report attempts to provide some of these data for carbohydrate and lipid metabolism and the steroid norgestrel. It has been shown that this 19-norprogestogen does not appear to significantly alter the blood fasting triglyceride or cholesterol levels. In contrast, there is a progressive alteration in carbohydrate metabolism with elevations of both blood glucose and plasma insulin levels. After one year, 15.5 per cent of the individual glucose tolerance tests are borderline abnormal to abnormal whereas after six months only 10.1 per cent were so altered.[1]

The significance of these data relate to two areas. First, it would appear that by reducing only the estrogen component of the contraceptives, carbohydrate abnormalities will persist. Second, if one is concerned about the atherogenic potential hazards of steroid contraceptives such as weight gain and changes in blood lipids, carbohydrates, and blood pressure, then the type and dose of the progestogenic steroid also must be considered. Recent evidence indicates that atherogenic sequelae, such as coronary thrombosis, are increased in oral contraceptive users.[2, 3] In view of this, study and development of steroid contraceptives must continue.

We would like to express their appreciation to Ms. G. Blumm, B. Heiser, S. Hitchcock, K. Holsinger, S. McCreary, Mr. G. Harris, and Dr. A. G. McLeod for their help in conducting these studies. We also wish to thank Mrs. J. Cassady for her assistance in performing the statistical calculations.

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Endometriosis in the black woman

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Endometriosis has heretofore been considered rare in black women. Laparoscopy in 190 black women, in many of whom pelvic inflammatory disease was previously diagnosed clinically and treated, revealed endometriosis to be present in 21 per cent. The importance of this finding for clinical practice is discussed.

THE TRADITIONAL criteria for the differential diagnosis of pelvic pain in the black woman may yield inaccurate diagnoses and result in clinical situations in which optimal care may not be given. The assumption that pelvic pain is almost invariably a consequence of pelvic inflammatory disease in these women may be the overriding basis of this problem.

This report details the characteristics of a series of black patients determined to have endometriosis by laparoscopy, with concentration on diagnostic criteria as relating to presenting signs and symptoms. This information can be expected to improve gynecologic care of affected patients by emphasizing the need for greater diagnostic accuracy.

Material and methods

During the four-year interval from 1971 to 1974, 190 diagnostic laparoscopies were done in black patients in a private-practice setting. Indications included both acute and chronic pelvic pain, primary and secondary infertility, dyspareunia, menorrhagia, metrorrhagia, amenorrhea, and the presence of an adnexal mass or nodularity. Several of these symptoms usually were present.

Although biopsies were neither done nor deemed necessary in establishing histologic diagnoses in the presence of obvious gross lesions, photographic documentation was accomplished in most cases.

Results

Forty of the 190 patients in this series (21.1 per cent) demonstrated laparoscopic evidence of endometriosis. Six of them had coexistent pelvic inflammatory disease. Many had had prior clinical diagnosis of pelvic inflammatory disease (37.5 per cent known), although not all had been completely informed about the details of past gynecologic diagnosis and treatment. Most of these patients had been treated ineffectually with antibiotics on one or more occasions. The palpable endometriomas had been misdiagnosed in at least one woman as uterine fibroids.

Age and parity distribution (Table I) was not dissimilar from that seen in series of white patients with endometriosis. Ages ranged from 18 to 40 years; five were teen-agers. Twenty-three had never conceived; of the 17 who had, five had had spontaneous abortions.

Some form of pelvic pain was the most frequent presenting complaint in this series (Table II), occurring in 28 patients (70.0 per cent). It was manifest usually as dyspareunia, dysmenorrhea, and/or spontaneous lower abdominal pain. Thirteen patients (32.5 per cent) had abnormal vaginal bleeding; one had severe metrorrhagia only.

The endometriotic lesions discovered at laparoscopy were distributed in expected locations (Table III), being encountered most commonly on the uterosacral ligaments, the cul-de-sac of Douglas, and the ovarian surfaces.

Comment

The value of laparoscopy in delineating the causes of pelvic pain and specifically in diagnosing endometriosis has been widely affirmed.[2, 3, 11] Of special interest here are the findings of Jacobson,[4] who found a 35 per cent rate of error associated with the preoperative clinical diagnosis of acute pelvic inflammatory disease in 814 patients.

Most textbooks of gynecology are in agreement[6–8, 12] that endometriosis is rare in the indigent nonprivate patient and, therefore, by inference (often stated as such) uncommon in the black woman. This could justifiably lead the student or physician in training to

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Table I. Age and parity distributions of patients with endometriosis

Age (years)	*No.*	*%*	*Parity*	*No.*	*%*
15-19	5	12.5	0	26	65.0
20-24	11	27.5	1	7	17.5
25-29	13	32.5	2	6	15.0
30-34	6	15.0	3	1	2.5
35-39	3	7.5			
40+	2	5.0			

Table II. Symptoms manifested by patients with endometriosis

Symptom	*No.*	*%*
Pelvic pain	20	50.0
Abnormal menses	13	32.5
Dysmenorrhea	10	25.0
Dyspareunia	5	12.0
Primary infertility	4	10.0
Secondary infertility	2	5.0
Comenstrual back and leg pain	2	5.0
Bowel changes	2	5.0
Asymptomatic	4	10.0

Table III. Sites of endometriosis determined at laparoscopy

Site	*No.*	*%*
Uterosacral ligaments	25	62.5
Cul-de-sac	17	42.5
Ovary	16	40.0
Fallopian tube	4	10.0
Round ligament	4	10.0
Vesicouterine fold	4	10.0
Bowel	4	10.0
Uterine serosa	3	7.5
Appendix	2	5.0
Broad ligament	2	5.0
Infundibulopelvic ligament	1	2.5

conclude that the search for endometriosis in black women would yield poor returns; thus the condition would not deserve to be included among the differential diagnostic possibilities, even in patients who present with compatible signs and symptoms.

Where racial differences specifically have been investigated, contradictory results have been encountered. Ridley,[9, 10] for example, concluded that the incidence of endometriosis was related to socioeconomic status rather than race. He cited Jeffcoate who had shown no real racial difference in the incidence of endometriosis. Lloyd,[5] in a study designed to evaluate the incidence of endometriosis in black women over a five-year period, reached similar conclusions. He showed essentially identical frequencies of endometriosis in black and white women, totalling 6.9 and 7.7 per cent, respectively. However, not all are in agreement.[1, 13]

Accepting the fact that this series of cases is constituted predominantly of private patients, we must purport that the results presented here clearly show that endometriosis is not rare in the black woman. Therefore, the clinician who is confronted with a black patient complaining of pelvic pain or symptoms compatible with endometriosis or who encounters abnormal findings on pelvic examination suggestive of endometriosis is obligated to pursue further his investigation. He should seriously consider laparoscopy in order to document or eliminate endometriosis as a possible etiologic factor. To relegate such patients categorically to the catch-basket of pelvic inflammatory disease without objective confirmation may condemn them to unnecessary, prolonged, and unrelieved discomfort, when in fact, their condition is otherwise readily amenable to definitive care if properly diagnosed.

When dealing with pelvic pain, abnormal vaginal bleeding, and/or abnormal suggestive pelvic findings in the black woman, physicians are urged to maintain an acute awareness that endometriosis does occur in black women. A high index of suspicion is needed. We should strive to eliminate any residual prejudicial diagnostic posture with reference to pelvic inflammatory disease. Routine rectovaginal examinations are important for more accurate diagnosis. Moreover, liberal use of diagnostic laparoscopy is essential.

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Review Course in Obstetrics and Gynecology

Columbia University College of Physicians & Surgeons announces its annual postgraduate course entitled, "Review Course in Obstetrics and Gynecology," to be held at Columbia-Presbyterian Medical Center, Monday through Friday, October 25-29, 1976. Some of the speakers are Drs. R. Vande Wiele, R. Richart, R. Neuwirth, associates, and guest lecturers. It will include a survey of the major clinical and pathologic problems pertaining to the female reproductive system. Emphasis will be on the diagnosis and management of obstetric and gynecologic disorders, including infertility, endocrine problems, and malignant diseases, with the use of modern advances in basic knowledge and clinical practice. There will be a review of gynecologic pathology. The course is divided as follows: gynecologic oncology, perinatal medicine, gynecology and obstetrics, reproduction control behavior, and endocrine disorders. The fee is $250 (residents $125). For registration, write to: Jose M. Ferrer, Jr., M.D., Associate Dean, 630 W. 168th St., New York, New York 10032. Telephone: (212) 694-3682.

Mucinous tumors of the ovary

II. Ultrastructural features of mucinous cystadenocarcinomas

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On the basis of light microscopic and scanning and transmission ultrastructural observations, ovarian mucinous tumors of borderline malignancy contain two types of mucinous epithelium—an endocervical type and an intestinal type. The fully malignant tumors were composed solely of intestinal-type epithelium. These findings may have prognostic and therapeutic significance.

THERE HAVE been numerous reports describing various clinical and histopathologic aspects of benign and malignant neoplasms of the ovary, but the ultrastructural features of these lesions have received little attention. To date, only two prior studies dealing with the ultrastructure of mucinous tumors have appeared[3, 7]; both dealt with the fine structure of the benign mucinous epithelium. The present study was undertaken to examine the ultrastructural features of malignant mucin-producing neoplasms of the ovary and to compare them with their benign counterparts.

Material and methods

The tissues used in this study were obtained fresh in the operating room from ten ovarian mucinous cystadenocarcinomas.

Light microscopy. In addition to the routine histopathologic examination, histochemical stains for mucin (mucicarmine, azure A, Alcian blue, and periodic acid–Schiff were obtained.[2] Only those carcinomas which stained positively for mucosubstances were included in this study. Autofluorescent studies were performed in each of the cases according to a method previously described.[3]

Scanning electron microscopy (SEM). The tissues for SEM were washed in 5 per cent acetic acid and then

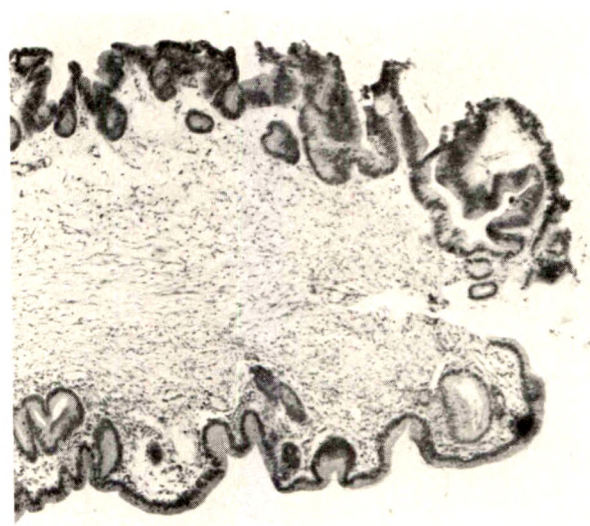


Fig. 1. Borderline malignancy. Portion of neoplasm illustrating an area of carcinoma in situ (top) in an ovarian mucinous tumor. The surrounding epithelium is of the intestinal type. Note the complex glandular structure of the area of carcinoma in situ (which resembles colonic neoplasms) and compare it to the single-cell lining of the benign portion of the cyst. (Alcian blue and periodic acid–Schiff. Original magnification ×200.)

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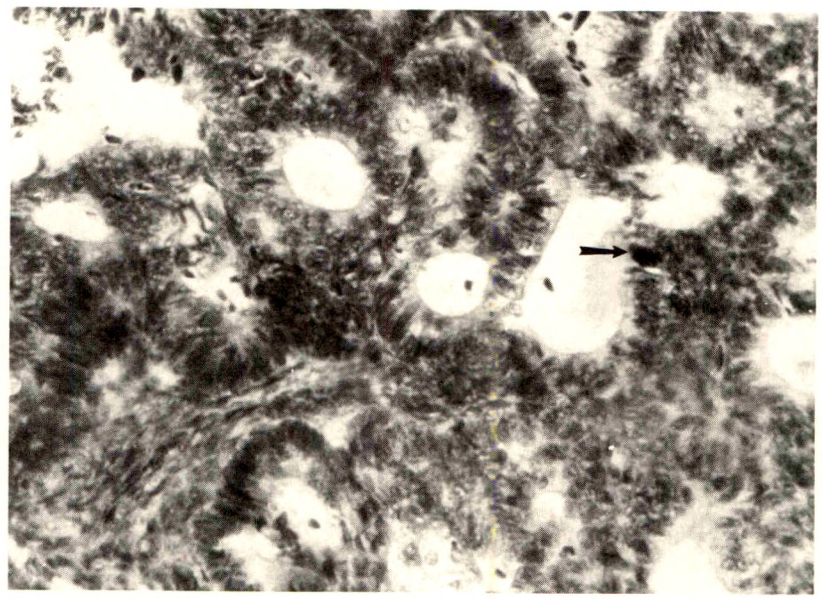


Fig. 2. Moderately well-differentiated carcinoma. Mostly solid neoplasm composed of back-to-back proliferation of neoplastic epithelium in which the glandular pattern is readily apparent. Mucin-producing cells are present (arrow). (Mucicarmine. Original magnification ×500.)

in phosphate-buffered saline (PBS). They were cut into 1 sq. cm. pieces and fixed in 2 per cent glutaraldehyde for 24 to 48 hours. The specimens were dehydrated, critical point dried as previously described,[4] and examined in a JSM-U3 scanning electron microscope. Following SEM examination, the specimens were removed from their stubs and processed for routine histology according to methods described in a previous communication.[3]

Transmission electron microscopy (TEM). The fresh tissues were minced into 1 mm. cubes and fixed in 2 per cent glutaraldehyde. They were processed as previously described[4] and examined in a JEM 7A transmission electron microscope.

Results

Light microscopy. The major clinical and pathologic features of the cases studied are summarized in Table I. The cytologic features directly correlated with the degree of differentiation and have been so tabulated.

Borderline malignancy (Cases 1 and 2). Two of the ten neoplasms fulfilled the criteria for borderline malignancy.[5] The majority of the epithelium was composed of endocervical-type mucinous cells and intestinal-type cells similar to those present in mucinous cystadenomas.[3] This epithelium was arranged in papillary folds with extensive aborizations into the cyst lumina. The areas of borderline malignancy (carcinoma in situ) were confined to the intestinal-type epithelium (Fig. 1). The areas of carcinoma in situ bore a striking histologic similarity to those of carcinoma in situ occurring in the colon. The glands were crowded together and had a branched appearance. The epithelium within this complex glandular pattern was composed of tall pencil-shaped, intermediate-type intestinal cells. Goblet cells were not present in these areas. Case 2 also contained areas of borderline serous cystadenocarcinoma. The distinction between the mucinous and serous areas of this neoplasm was striking when the sections were stained for mucin. The epithelium in both of the cases was multilayered; the nuclei were cytologically atypical, and stromal or capsular invasion was absent.

Well-differentiated carcinomas (Cases 3 to 5). All three neoplasms contained mature and immature intestinal-type epithelial cells as well as argentaffin and goblet cells. Endocervical cells were not identified. The epithelium had a stratified appearance, and many areas were histologically identical to those seen in well-differentiated colonic carcinomas. In such areas, the stratified cells resembled the immature, pencil-shaped, colonic absorptive cells and intermediate cells, and well-developed goblet cells were scarce. Stromal invasion was present. There was a greater degree of pleomorphism than was noted in the borderline tumors, and the papillary, intracystic, glandular proliferations were slightly more complex.

Case 5 was associated with a well-differentiated

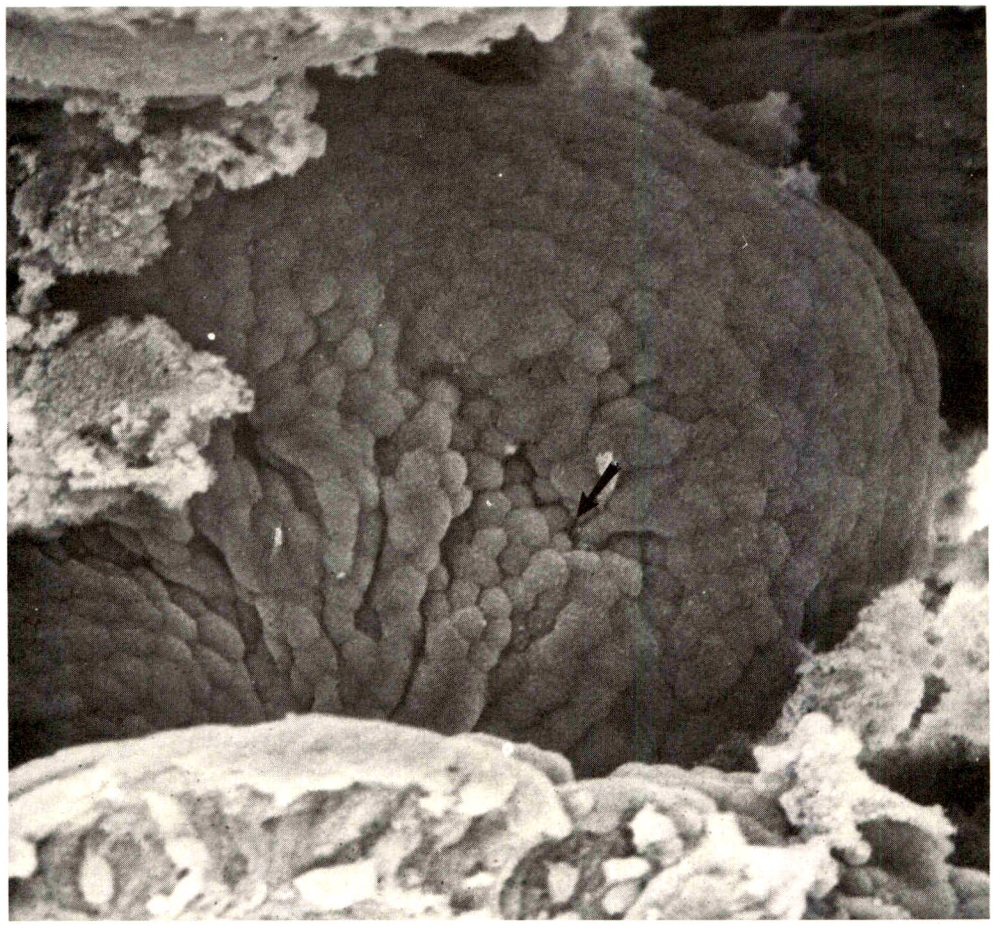


Fig. 3. Scanning electron micrograph. Borderline malignancy. The upper portion of the picture corresponds to the benign portion of the cyst which is lined by pentagonal cells with a regular arrangement. In the lower portion of the picture, distortion of this pattern is produced by formation of intracystic ridges corresponding to the areas of carcinoma in situ. The junction of the benign and malignant epithelium is indicated by the arrow and was verified by examination of the rehydrated SEM specimen. (×700.)

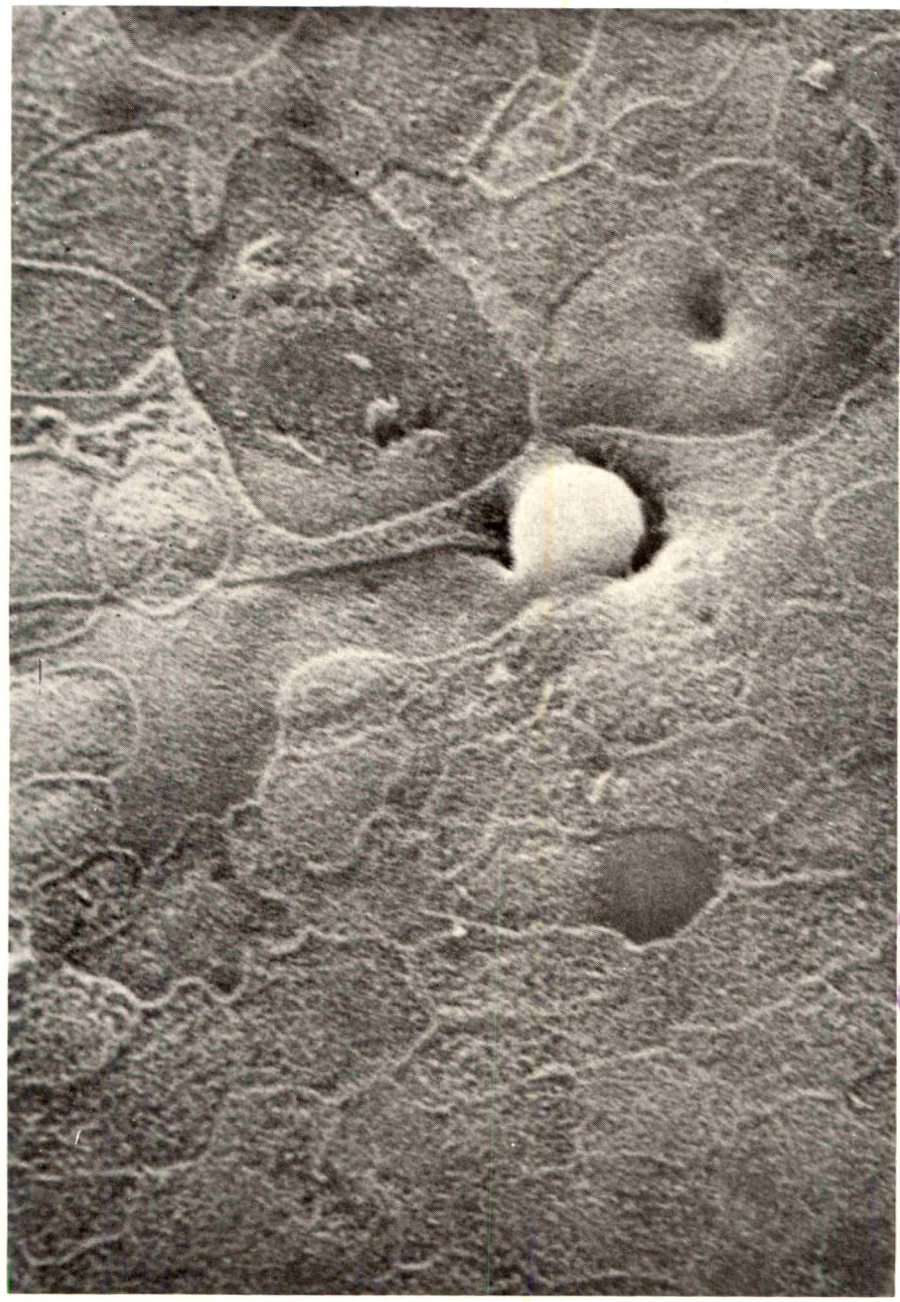
serous cystadenocarcinoma, and, in the serous areas, numerous ciliated cells were identified.

Moderately well-differentiated carcinomas (Cases 6 to 8). These neoplasms were characterized by solid anaplastic cellular proliferations in which complex gland-in-gland formations and sparse intervening connective tissue stroma were seen. Only rare mature goblet cells were identified. The lesions histologically bore a striking resemblance to moderately well-differentiated colonic carcinomas. Stains for mucosubstances highlighted the presence of some of the goblet cells within the glandular proliferations (Fig. 2). Many immature goblet cells with small apical mucin droplets were also encountered. In addition, argentaffin cells were identified in two of the three cases. Endocervical cells were not noted.

Poorly differentiated carcinomas (Cases 9 and 10). These specimens were both composed predominantly of solid sheets of anaplastic cells. A glandular pattern was focally present but difficult to identify in most areas. It was not possible to identify the majority of cell types, but histochemical stains for mucin were focally positive. Occasional signet-ring cells were also identified. Endocervical cells and argentaffin cells were not identified in either neoplasm.

SEM.

Borderline tumors. The cystic spaces of borderline tumors were lined by regular, pentagonally shaped epithelial cells which were thrown up into short intracystic ridges (Fig. 3). The cells were of uniform size and pentagonal shape, and both endocervical and intestinal types of mucinous epithelial cells were identified. They resembled those seen in the mucinous cystadenomas.[3] The intervening non–mucin-pro-



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Fig. 4. Scanning electron micrograph. Moderately well-differentiated carcinoma. A population of pleomorphic cells is present. Note the irregular size and shape of these cells. A mucin-secreting cell is present. (×1,400.)

ducing cells were covered with a lush microvillous surface. In the areas of Case 2 which corresponded to a borderline serous cystadenocarcinoma, numerous ciliated cells were identified. These were not present in other areas of this neoplasm, and they were not present in Case 1.

Well-differentiated carcinomas. The over-all architecture of these lesions was that of a disorderly array of cells which were more stratified than those in the borderline tumors. The majority of the cells were covered with a well-developed microvillous surface, but mucin-secreting cells were interspersed among them. Unlike the cells present in the borderline tumors, the cells were no longer uniformly pentagonal, and their

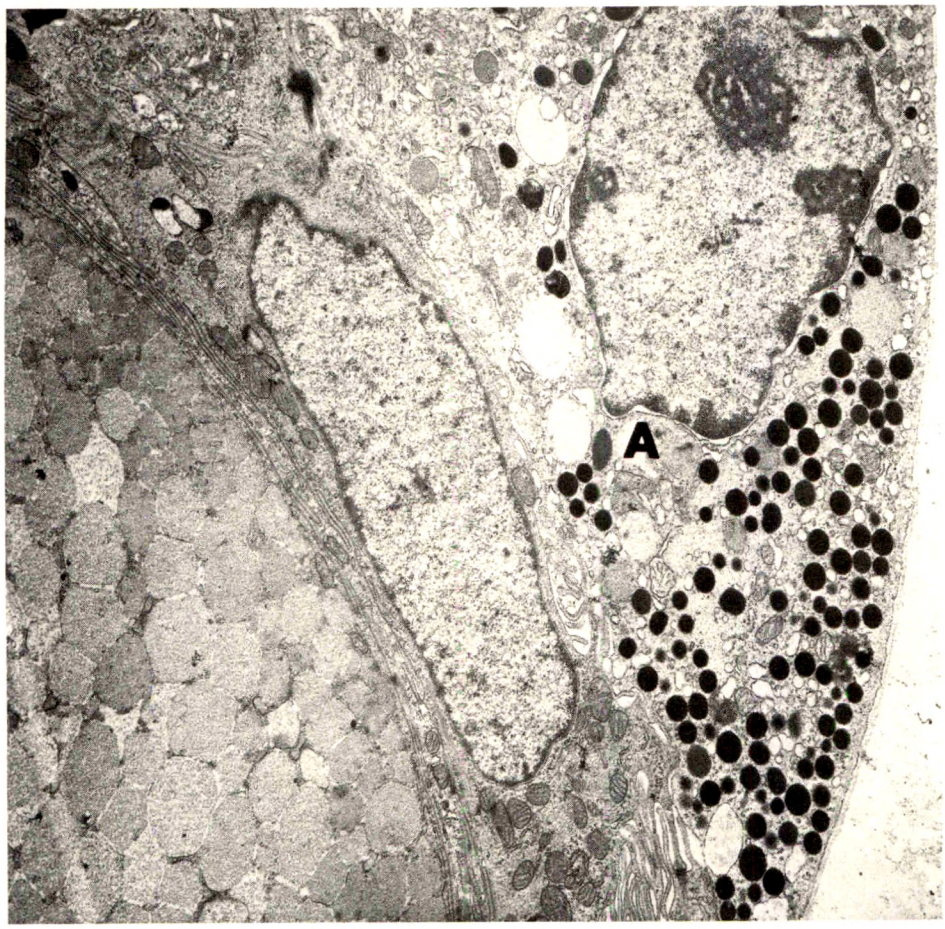


Fig. 5. Transmission electron micrograph. Borderline malignancy, area of carcinoma in situ. Intestinal-type cells with an argentaffin cell *(A)*, an intestinal absorptive-type cell, and a mucin-secreting cell. (×174,000.)

size was variable (Fig. 4). Ciliated cells were not noted in any of the neoplasms except in Case 5, in which they were confined to the areas of serous cystadenocarcinoma.

Moderately well-differentiated carcinomas. Only one of the neoplasms was satisfactory for SEM examination. In this case the cells were extremely variable in both size and shape with irregular cell borders. Some of the cells were 3 to 4 times normal size, and many were smaller than normal. Rare mucin-producing cells were identified, and, where present, the mucin droplets were always smaller than those seen in better-differentiated neoplasms.

Poorly differentiated carcinomas. It was not possible to study the surface of the poorly differentiated carcinomas because of the large amount of necrosis, hemorrhage, and surface debris.

TEM.

Borderline tumors. In the benign areas of these neoplasms, the papillary infoldings of the epithelium were lined by endocervical cells, rare mature absorptive cells, goblet cells, immature absorptive cells, immature goblet cells, intermediate cells, and argentaffin cells (Fig. 5). In both tumors, the cells in the areas of carcinoma in situ were stratified with loss of polarity. These areas were composed solely of immature colonic-type absorptive cells characterized by numerous supranuclear mitochondria, extensive Golgi zones and granular endoplasmic reticulum (GER), moderately complex interdigitating lateral margins, and long microvilli. The latter were anchored to the apical portions of the cells by long microfilamentous rootlets and were covered by a thick glycocalyx (Fig. 6). The area immediately below the apical surface was devoid of most cellular organelles except the microfilamentous rootlets. The intercellular spaces were dilated at the basal ends of the cells, and the apical ends were closed by desmosomes and tight junctional complexes.

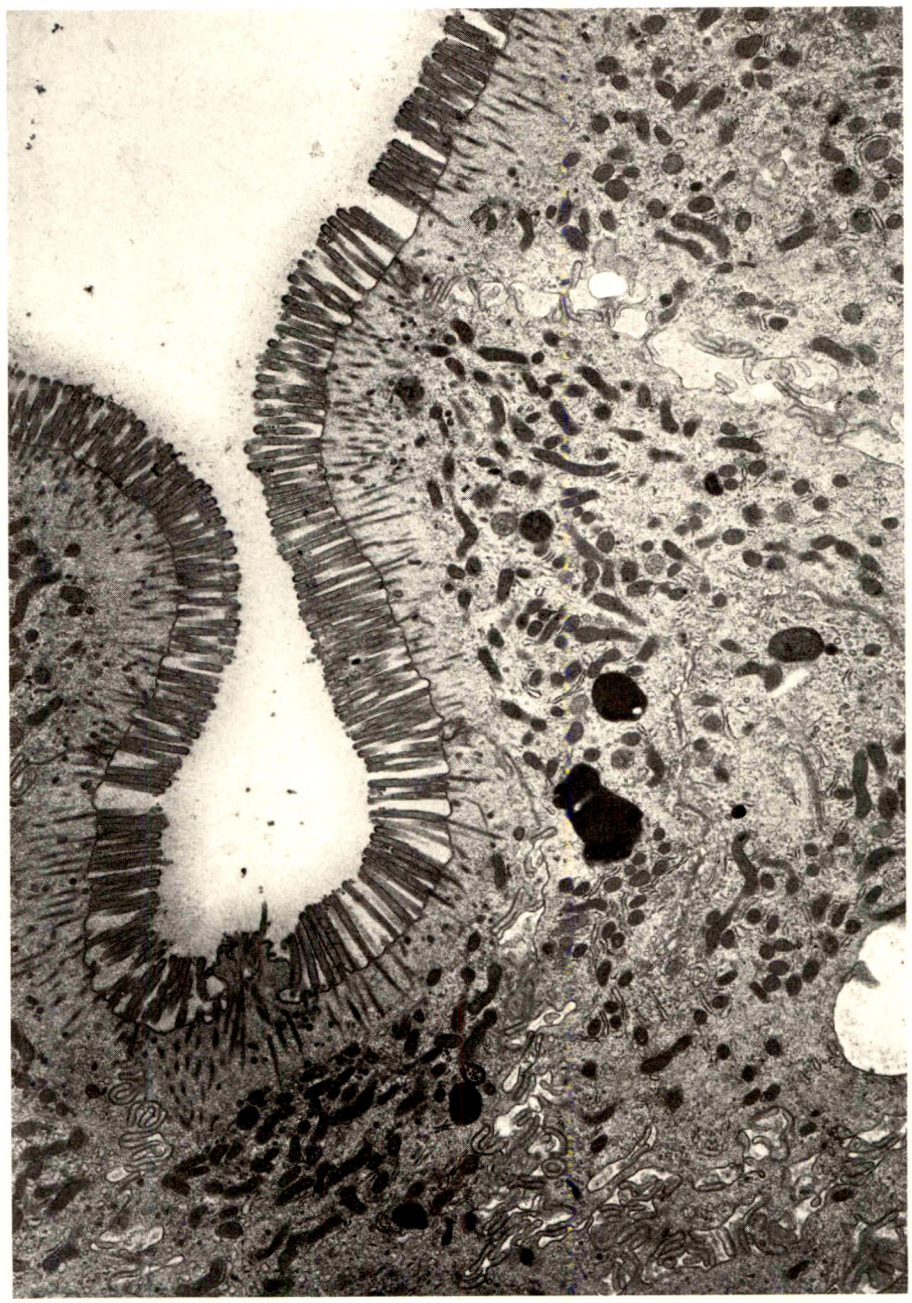


Fig. 6. Transmission electron micrograph. Borderline malignancy, area of carcinoma in situ. Portions of several immature absorptive-type cells with prominent mitochondria, long microvilli, and dense glycocalyx. (×4,200.)

Ciliated cells were only identified in those areas corresponding to the serous component in Case 2.

Well-differentiated carcinomas. The frankly invasive carcinomas were composed exclusively of intestinal-type epithelium. Endocervical cells were absent. The immature epithelial cells focally maintained their polarity, and the majority of the mucinous secretions were confined to apical droplets within immature goblet cells (Fig. 7). Ciliated cells were only present in Case 5 in areas with serous differentiation. The lateral cell margins were quite complex with extensive interdigitations, and the intercellular spaces were frequently dilated. The nuclei were elongated and contained rare cytoplasmic invaginations. The

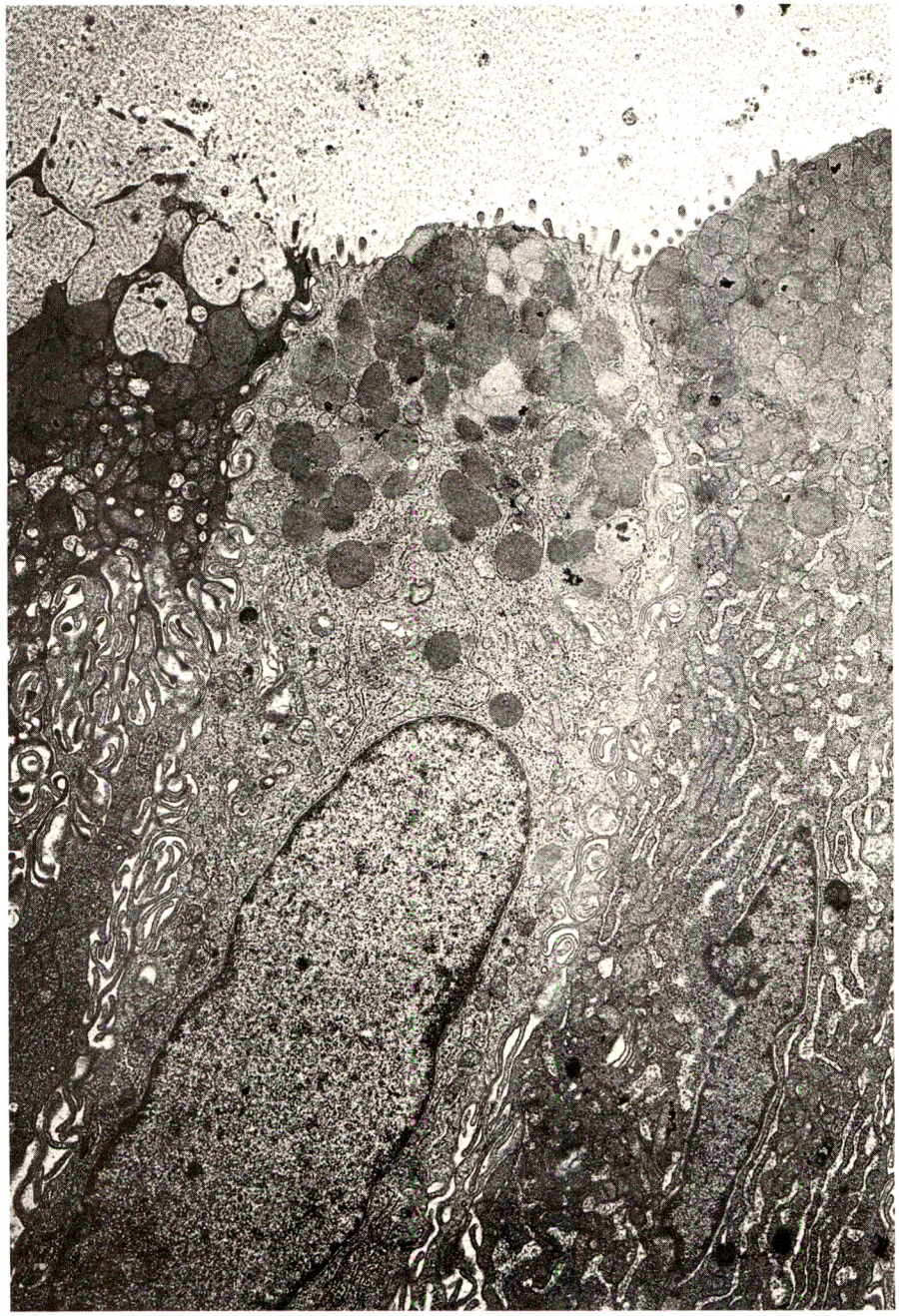


Fig. 7. Transmission electron micrograph. Well-differentiated carcinoma. Note tall columnar cells which have maintained their polarity and contain apical cells of mucin secretion. (×7,600.)

cells were covered with short, irregular microvilli.

Moderately well-differentiated carcinomas. These neoplasms were composed almost exclusively of immature cells which no longer had a columnar shape but appeared rounded and broadened. (The only mature cell type identified was a rare argentaffin cell.) The cells were arranged in disorderly multilayers, with loss of polarity. The cells in the upper layers contained mucinous secretory vacuoles whereas the cells beneath them appeared totally undifferentiated without obvious secretory activity. These immature cells were round and contained abundant GER, free ribosomes, mitochondria, and Golgi zones. The mitochondria were pleomorphic. The cells had a wide range of sizes



Fig. 8. Transmission electron micrograph. Poorly differentiated carcinoma. Anaplastic cell with irregular microvillous surface and small number of poorly formed mucin droplets and lysozomes. (×8,000.)

and shapes, and the nucleocytoplasmic ratio was increased. The nuclei were rounded with numerous cytoplasmic invaginations.

Poorly differentiated carcinomas. The majority of these neoplasms were composed of immature cells of an indeterminate type. There was a wide range in cell size and shape, and the nuclei were enlarged with a high nucleocytoplasmic ratio. The nuclei had irregular complex shapes with numerous cytoplasmic invaginations. Extensive cytoplasmic accumulations of glycogen, autophagosomes, lipid droplets, and myelin figures were present. These cells were present in large cellular sheets with little intervening connective tissue stroma. An occasional anaplastic cell containing poorly

Table I. Mucinous cystadenocarcinomas—pathologic findings

Case No.	*Age of patient*	*Side*	*Gross appearance*	*Light microscopic features*	*Associated lesions in same ovary*	*TEM*
1	56	Right ovary	21 by 17 by 15 cm., 1,800 grams, multilocular	Borderline malignancy, mixed endocervical and intestinal cells	None	Mixed intestinal- and endocervical-type cells
2	45	Right ovary	3 by 6 by 3 cm., unilocular with papillary projections	Borderline malignancy, mixed endocervical and intestinal cells. Serous component	None	Mixed endocervical-, intestinal-, and ciliated serous–type cells
3	17	Left ovary	Multilocular, 600 grams	Well-differentiated carcinoma, intestinal cells only	None	Mature and immature intestinal-type cells
4	61	Right ovary	Multilocular, solid areas, 1,000 grams	Well-differentiated carcinoma, intestinal cells including goblet cells	Benign mucinous adenoma	Intestinal-type cells
5	41	Bilateral	Left—4 by 12 by 15 cm., 470 grams; Right—3 by 8 by 12 cm., 260 grams	Well differentiated mucinous and serous carcinoma. Goblet and ciliated cells	None	Mature and immature intestinal, undifferentiated and ciliated cells
6	56	Bilateral	Left—5 by 4 by 3.5 cm., solid; Right—12 by 15 by 3 cm., partly solid	Moderately well-differentiated carcinoma, intestinal cells	None	Mostly immature intestinal-type cells
7	62	Bilateral	Solid necrotic tissue	Moderately well-differentiated carcinoma, many signet-ring cells	Cortical Inclusion cysts	Immature intestinal-type cells
8	51	Right ovary	8.4 by 7.9 by 5.3 cm., solid	Moderately well-differentiated carcinoma	None	Immature intestinal-type cells
9	51	Right ovary	Multilocular, partly solid, 750 grams	Poorly differentiated carcinoma, mucinous lakes	None	Very immature cells with abortive mucin production
10	47	Right ovary	Large solid mass extending to adnexa, 6.5 by 3.5 by 3.0 cm.	Poor differentiated carcinoma	None	Mostly immature cells, rate mucin-producing cells

formed mucin droplets was identified (Fig. 8). Luminal spaces were not identified.

Comment

The differentiation of the mucinous cystadenocarcinomas examined in this series ranged from borderline malignancy to so poorly differentiated that without the use of histochemical stains for mucin they would not have been classified as mucinous carcinomas. (The specific result of these histochemical studies is the subject of another article.[2])

The benign areas of the borderline lesions resembled the mucinous cystadenomas of the mixed endocervical-intestinal type.[3] The carcinomatous areas were composed solely of intestinal epithelium. Like the mucinous cystadenomas,[3] ciliated cells were absent in the mucinous carcinomas unless a serous component was also present. The ultrastructural features of the serous component were similar to those of the pure ovarian serous cystadenomas.[1]

In all of the well-differentiated and moderately well-differentiated mucinous carcinomas, the various intestinal epithelial cell types which were noted in the mixed-type mucinous cystadenomas were present. With increasing histologic grade, the individual cells become increasingly immature, and the organization of these cells becomes increasingly chaotic. The ease with which mature intestinal cells could be identified was directly proportional to the differentiation of the neoplasm.

The most significant finding was the apparent absence of endocervical-type mucinous cells in the frankly malignant tumors. Endocervical-type cells were present in both cases of borderline malignancy, but

SEM	*Argentaffin cells*	*Other*
Regular	Yes	Inactive endometrium
Regular with occasional ciliated cells	Yes	None
Irregular	Yes	None
Irregular	No	Omental metastases
Irregular	No	None
Irregular	Yes	Endometrium retrogressive, cystic, glandular hyperplasia
Specimen not adequate	Yes	Omental metastases, endometrial polyp with cystic glandular hyperplasia
Specimen not adequate	Yes	None
Specimen not adequate	No	None
Specimen not adequate	No	Omental metastases

they were relatively rare in comparison to the mixed-type mucinous cystadenomas. The majority of the cellular population was composed of immature absorptive cells. The lack of endocervical-type cells in the mucinous adenocarcinomas sharply contrasts with findings in the mucinous cystadenomas, all of which contained endocervical-type cells either alone or in combination with intestinal-type epithelium.

It is difficult to explain why all the carcinomas in this study were composed of intestinal-type epithelium when such epithelium is present in only 25 per cent of the mucinous cystadenomas and why there were no carcinomas with the endocervical type cells when that cell type is present in 100 per cent of the benign mucinous neoplasms. However, it may be important that the intestinal-type epithelium encountered in the mucinous cystadenomas is of the immature type generally found in colonic adenomas and known to be heir to a high rate of malignant transformation in its colonic location whereas the endocervical-type epithelium is of the mature type found in the adult endocervix and uncommonly becomes malignant. The colonic epithelium may also have a higher rate of proliferation than the endocervical component in the mixed-type tumors, and the former may gradually overgrow the latter and form a larger susceptible population.

The relatively high proportion of mucinous cystadenomas which are composed solely of endocervical cells may account for the low incidence of malignancy in the mucinous neoplasms when compared to the serous tumors. Endocervical cells may normally have a low malignant potential (as in the normal endocervix), and this may also be true of endocervical cells in an ovarian site.

If it were possible to distinguish prospectively the purely endocervical-type mucinous tumor from the mixed type which contains an intestinal component, the malignancy rate in the two would probably be strikingly different. In any case, the recognition that the mucinous carcinomas of the ovary are colonic cancers may be important clinically, and diagnostic and chemotherapeutic regimens which are effective in colon carcinomas should be evaluated in their ovarian counterparts.

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Differential ovarian and adrenal vein catheterization

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Twenty-two hirsute women underwent percutaneous adrenal and ovarian vein catheterization to differentiate and localize excessive hormonal output. All studies were done under fluoroscopic control; catheter placement was verified by venography, and blood samples were withdrawn for hormonal analysis. The right ovarian vein was successfully sampled in 42 per cent of attempts; the left ovarian vein, in 75 per cent; the right adrenal vein, in 56 per cent; and the left adrenal vein, in 100 per cent. Bilateral catheterization did not prove clinically useful. First, anatomic variations in venous size and drainage made catheterization and bilateral sampling difficult. Second, adrenal secretion is both episodic and parallel, necessitating both simultaneous catheterization and serial sampling for adequate diagnosis. The stress of the procedure may provoke increased adrenal output. Third, since ovarian secretion is not parallel, and since increased hormone output has been documented in that ovary containing developing follicles or a corpus luteum, distinguishing ovarian dysfunction proved difficult. Finally, for a time-consuming procedure, patient discomfort cannot be disregarded. This technique has not proved to be a reliable means of determining the site of androgen hypersecretion and thus cannot be recommended in the routine evaluation of female hirsutism.

SEVERAL REPORTS have described the efficacy of differential ovarian and adrenal vein catheterization in evaluating the etiology of female hirsutism. Kirschner and Jacobs[1] demonstrated an ovarian source for excessive androgens in the majority of hirsute patients, although they concluded that catheterization data were subject to large errors and should be accepted as a crude attempt at a fine measurement. Judd and co-workers,[2] in a patient who had virilization in pregnancy, obtained levels of testosterone and androstenedione in the right ovarian vein higher than those in the vena cava. At operation, the patient was found to have bilateral theca lutein cysts. The same workers localized a testosterone-secreting ovarian tumor preoperatively and concluded that retrograde catheterization and selective venous sampling can be used effectively.[3] Stahl and associates[4] investigated 16 hirsute women and three nonhirsute patients by percutaneous venous sampling and measurement only from the left adrenal and ovarian veins. Eight patients had elevated androgens of adrenal origin; five had combined adrenal and ovarian hypersecretion, and two had elevated serum testosterone of peripheral origin. The authors concluded that this method of testing is relatively simple, is associated with no morbidity, and does not require lengthy, potentially inaccurate suppression and stimulation studies. Northrop and colleagues[5] used a similar protocol to investigate 19

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Table I. Clinical findings in nine patients who underwent exploratory ovarian operation. Normal values (excluding sampling during the periovulatory surge): FSH, 150 to 350 ng. per milliliter; LH, 30 to 90 ng. per milliliter.

Case no.	*Age (yr.)/ parity*	*Height (inches)/ weight (pounds)*	*Menses*	*Degree of hirsutism*	*Pelvic examination*	*Maturation index*	*FSH/LH (ng./ml.)*	*Diagnosis*
1	24/0	64/236	R	Marked	↑ Right ovary	—	N.L.	Theca luteinization, follicle cysts
2	20/0	64/176	2° A	Marked	N.L.	0/98/2	292/62	PCO
3	18/0	67/132	2° A	Mild	N.L.	100/0/0	253/92	Bilateral hyperthecosis
4	31/0	68/165	R	Mild	↑ Left ovary	—	N.D.	Bilateral hyperthecosis
5	18/0	63/233	2° A	Marked	Nonpalpable	40/60/0	200/45	Lipoid tumor, left ovary
6	28/0	68/210	2° A	Mild	N.L.	0/90/10	271/164	PCO
7	15/0	64/240	1° A	Mild	↑ Left ovary	60/40/0	216/94	PCO and hyperthecosis with corpus luteum cyst
8	18/0	67/193	Irregular	Mild	↑ Right ovary	—	N.D.	
9	27/0	61/194	2° A	Marked	N.L.	0/90/10	295/195	Bilateral hyperthecosis

R = Regular menses; A = amenorrhea; PCO = polycystic ovaries; N. D. = not done; N.L. = normal limits.

hirsute women. Steroid levels were not reported, but similar conclusions were reached. Our experience with the technique and the interpretation of the hormonal data have differed from the success described by these authors. This report constitutes a summary of our experience with bilateral adrenal and ovarian vein catheterization in 22 hirsute women.

Material and methods

Clinical population. Twenty-two women with hirsutism were admitted to the Clinical Research Center and evaluated by a catheterization procedure. Initial studies included urinary 17-ketosteroids, 17-hydroxysteroids, and plasma testosterone, repeated during dexamethasone (DXM) administration. Five patients had bilateral ovarian and adrenal vein catheterization while not receiving medication, and three of them had a second study after administration of DXM, 1.25 mg. per 100 pounds of body weight, for at least five days. Seventeen additional women had only differential catheterization after six to eight days of DXM administration.

Nine of the twenty-two women, one of whom had catheterization twice, had exploratory laparotomy. Their clinical details and ovarian pathologic diagnoses are shown in Table I.

Catheterization technique. All differential catheterization studies were carried out by one of us (R. I. W.) in the Cardiovascular Diagnostic Laboratory with local anesthesia; the Seldinger approach from either or both femoral veins, as described by Kirschner and Jacobs,[1] was used. All studies were done with fluoroscopic control, and catheter placement was verified by venography. All adrenal venograms were within normal limits. Blood samples were obtained, with the use of slight back pressure, from the inferior vena cava, the left and right adrenal veins, and the left and right ovarian veins. A peripheral blood sample was usually obtained simultaneously with the first specimen. In most cases, a research nurse was assigned to note the time that samples were collected, the duration of the procedure, and the complications or problems encountered.

Hormonal assays. Plasma testosterone and androstenedione were measured by radioimmunoassay.[6, 7] Plasma cortisol was determined by the method of Beitins and co-workers.[8] Urinary 17-ketosteroids (17-KS) and 17-hydroxysteroids (17-OH) were determined by the methods of Glenn and Nelson[9] and Callow and colleagues.[10]

Results

Endocrine findings in 13 patients who did not undergo operation are shown in Table II. Fifteen catheterization studies were performed, but the first study in No. 11 did not involve an attempt to obtain ovarian blood samples. In the remaining 14 procedures, no blood was obtained from the right ovarian vein in 3 of 14 attempts; insufficient blood was obtained in 1 of 14, and the sample could only be obtained at the vein orifice in 6 of 14. Thus, an adequate sample from the right ovarian vein was obtained in 4 of 14 studies (29 per cent); from the left ovarian vein, in 9 of 14 (64 per cent); from the right adrenal vein, in 8 of 15 (53 per cent); and the left adrenal vein, in 100 per cent. In several patients, however, left adrenal vein values were similar to caval values, suggesting that in these cases samples were not

Table II. Endocrine findings in 13 patients who did not undergo operation. Results in the first four columns indicate the urinary and plasma steroids before and during DXM suppression. The remaining columns show hormonal values obtained during differential catheterization and whether the procedure was done with the patient receiving no medication or DXM

Case no.	Medication	Urinary steroids		Plasma T (ng./100 ml.)	Hormone measured	Peripheral	Vena cava	Ovarian vein	
		17-KS	17-OH					Right	Left
10	0	10.2	3.6	232	T	N.S.	219	469*	179*
					A	N.S.	683	761*	843*
					C	N.S.	13.2	10.0*	10.8*
	DXM	1.8	0.2	219	T	N.S.	170	179*	157*
					A	N.S.	991	611*	381*
					C	N.S.	1.6	1.2*	0.8*
11	0	34.0	13.4	42	T	N.S.	91	N.S.	N.S.
					A	N.S.	332	N.S.	N.S.
					C	N.S.	22.0	N.S.	N.S.
	DXM	8.0	3.5	37	T	35	49	65*	68
					A	–	319	299*	310
					C	6.8	18.0	20.1*	21.3
12	0	20.9	8.6	63	T	63	N.S.	161	91*
					A	245	N.S.	1,678	288*
					C	9.6	N.S.	7.8	3.6*
13	0	9.8	12.7	108	T	N.S.	106	558	1,229
					A	N.S.	501	3,012	4,292
					C	N.S.	12.0	12.0	12.0
	DXM	3.1	0.8	89					
14	0	21.3	7.7	126					
	DXM	5.2	1.4	114	T	82	93	166	75
					A	379	617	2,277	454
					C	0.2	0.4	0.8	0.4
15	0	13.5	9.5	78					
	DXM	3.7	0.9	51	T	51	68	N.B.	N.B.
					A	—	—	N.B.	N.B.
					C	0.6	3.0	N.B.	N.B.
16	0	17.3	7.9	59					
	DXM	4.5	0.2	95	T	56	28	N.B.	26
					A	—	135	N.B.	115
					C	0.7	3.0	N.B.	0.2
17	0	9.7	11.7	60					
	DXM	2.4	1.3	55	T	39	21	55*	82
					A	194	144	226*	1629
					C	1.4	0.8	1.0*	0.8
18	0	15.1	8.0	82					
	DXM	2.8	1.0	49	T	93	132	N.B.	77
					A	286	401	N.B.	304
					C	1.3	1.3	N.B.	1.6
19	0	—	—	69					
	DXM	—	—	—	T	N.S.	90	216*	106
					A	N.S.	439	3,436*	1,384
					C	N.S.	N.S.	N.S.	N.S.

*Sample collected from vein orifice. N.S., No sample collected; N.B., catheterized but no blood obtained; T, testosterone (normal limits: 49± 13 ng. per 100 ml.); A, androstenedione (normal limits: 181± 59 ng. per 100 ml.); C, cortisol (normal limits: 8 to 18 mg. per 100 ml.); 17-KS, 17-ketosteroids (normal limits: 4 to 13 mg./24 hours); 17-OH, 17-hydroxycorticosteroids (normal limits: 2 to 8 mg. per 24 hours).

Adrenal vein			
Right	*Left*		
107*	235		
154*	675		
8.8*	7.0		
158	136		
563	281		
3.6	1.2		
		+15 min.	*+30 min.*
1,161	1,203	676	281
10,952	12,094	4,974	1,038
875	757	80.2	32.0
Lost*	175		
307*	"too high"		
18.4*	219		
49*	163		
183*	1,090		
9.2*	23.1		
111	96		
542	423		
11.2	14.4		
108	62		
1,131	632		
0.4	8.8		
294	74		
—	—		
380	9.1		
N.B.	31		
N.B.	271		
N.B.	2.8		
35	33		
278	263		
2.6	3.0		
71	79		
293	337		
1.2	2.3		
N.B.	84		
N.B.	597		
N.B.	N.S.		

taken from the vein or that significant admixture had occurred.

After elimination of those studies in which only the adrenal vein orifice was sampled, a marked difference was observed between the right and left adrenal vein results in Nos. 14, 15, and 22. In No. 14, the right adrenal sample corresponded to vena cava values; in No. 22, no caval sample was collected for comparison; in No. 15, right adrenal venography was normal, suggesting that stress may have increased adrenal output.

In Nos. 10 and 11, two catheterization procedures were performed, before and while receiving DXM. In No. 10, DXM suppression suggested an adrenal etiology of androgen production since both 17-KS and 17-OH values were suppressed normally to less than 2.5 and 2.0 mg. per 24 hours, respectively.[11] Catheterization results were not confirmatory and even suggested DXM suppression of ovarian output, probably an artifact of sampling at the orifice. Values from the left adrenal vein probably reflect dexamethasone suppression of adrenal output. In No. 11, DXM suppression suggested an adrenal etiology, because of inadequate suppression of 17-OH values. Samples obtained from both adrenal veins show hypersecretion, but a marked decrease in steroid values was observed in the left adrenal vein over a 30 minute period with the catheter in place. Catheterization during administration of DXM suggested incomplete suppression of adrenal output, although definite sampling from the right adrenal vein was not accomplished. Left adrenal venography was normal. Results in the remaining patients were similarly analyzed. Only No. 18 was thought to have evidence of an adrenal etiology, not substantiated by catheterization results. Nos. 15, 20, and 22 appeared to have increased adrenal output of androgens, but, in two of them, ovarian sampling was inadequate for comparison. Only Cases Nos. 13 and 19 had studies which definitely pointed to an ovarian etiology.

The endocrine results in those patients who underwent exploratory laparotomy are shown in Table III. In all individuals, the decision for laparotomy was made independent of catheterization studies, on the basis of clinical findings and other hormonal indication. In these patients, the right ovarian and right adrenal vein were each catheterized in 60 per cent of attempts; the left ovarian vein, in 90 per cent; and the left adrenal vein, in 100 per cent. Thus, in the nine patients thought to have an ovarian indication for operation, bilateral ovarian vein sampling was accomplished in only five.

Table II—Cont'd.

Case no.	Medication	Urinary steroids		Plasma T (ng./100 ml.)	Hormone measured	Peripheral	Vena cava	Ovarian vein	
		17-KS	17-OH					Right	Left
20	0	13.8	6.7	59					
	DXM	3.4	1.0	30	T	30	20	33	23
					A	—	151	555	180
					C	—	N.S.	N.S.	N.S.
21	0	15.7	12.5	38					
	DXM	5.7	1.4	—	T	N.S.	Lost	N.B.	32
					A	N.S.	Lost	N.B.	129
					C	N.S.	Lost	N.B.	0.5
22	0	23.4	11.4	85					
	DXM	6.9	1.0	—	T	N.S.	N.S.	78*	66*
					A	N.S.	N.S.	415*	321*
					C	N.S.	N.S.	0.6*	0.7*

Table III. Endocrine findings in nine patients who underwent exploratory ovarian operation

Case no.	Medication	Urinary steroids		Plasma T (ng./100 ml.)	Hormone measured	Peripheral	Vena cava
		17-KS (ng./24 hr.)	17-OH (ng./24 hr.)				
1	0	5.6	10.4	290			
	DXM	2.4	0.5	342	T	342	481
					A	—	1,630
					C	1.6	1.6
2	0	24.5	7.0	92			
	DXM	6.7	0.2	106	T	106	99
					A	440	484
					C	1.2	1.0
3	0	5.3	2.7	314			
	DXM	4.9	1.8	388	T	415	289
					A	—	—
					C	1.2	7.2
4	0	19.1	9.9	97			
	DXM	2.4	1.3	54	T	N.S.	N.S.
					A	N.S.	N.S.
					C	N.S.	N.S.
5	0	30.8	9.6	332			
	DXM	12.6	1.3	453	T	288	N.S.
					A	1,345	N.S.
					C	0.5	N.S.
6	0	16.1	5.1	240			
	DXM	10.2	1.9	156	T	206	294
					A	—	547
					C	0.4	1.6
7	0	13.2	17.0	86			
	DXM	3.0	1.1	77	T	N.S.	68
					A	N.S.	211
					C	N.S.	18.0
8	0	13.5	12.7	113	T	N.S.	136
	DXM	6.0	1.3	N.S.	T	N.S.	73
9	0	16.2	6.8	163			
	DXM	15.8	1.5	319			
	Clomid, 50 mg. daily, Day 5	—	—	—	T	211	369
					A	—	—
					C	—	

N.S., No sample collected; N.B., catheterized but no blood obtained; T, testosterone (normal limits: 49 ± 13 ng. per 100 ml.); A, androstenedione (normal limits: 181 ± 59 ng. per 100 ml.); C, cortisol (normal limits: 181 ± 8 to 18 ng. per 100 ml.); 17-KS, 17-ketosteroids (normal limits: 4 to 13 mg./24 hours); 17-OH, 17-hydroxycorticosteroids (normal limits: 2 to 8 mg. per 24 hours).

*Sample collected from vein orifice.

Adrenal vein	
Right	*Left*
47*	52
507*	918
N.S.	N.S.
N.B.	48
N.B.	488
N.B.	16.9
89	58
1,325	311
14.8	0.6

Ovarian vein		*Adrenal vein*	
Right	*Left*	*Right*	*Left*
2,863*	N.B.	318	215
4,762*	N.B.	699	1,131
4.8*	N.B.	2.0	12.0
N.B.	145	N.B.	90
N.B.	1,147	N.B.	933
N.B.	1.3	N.B.	10.8
339	289	259	339
—	—	—	—
8.1	6.4	8.4	10.0
158	340	44*	52
2,383	3,033	352*	289
8.0	3.0	6.5*	5.0
626*	220	N.B.	241
5,842*	1,529	N.B.	2,584
2.6*	0.8	N.B.	37.5
293*	244	162	203
453*	574	301	306
2.0*	1.6	1.2	8.4
298	56	69	82
1,571	211	1,145	1,611
26	22	40	46
318	95	110	121
173	62	57	51
1057	593	226	234
—	—	—	—
7.7	5.7	5.3	36

In No. 5, results suggested an androgen-producing tumor of the right ovary. At surgery, the tumor was found to be in the left ovary. Mislabeling of tubes or switching of samples at the time of assay was not thought to have occurred. Left adrenal vein values were higher than those from the left ovary, suggesting that the sample thought to be from the left ovarian vein was obtained from the vena cava, as the results are consistent with peripheral values.

In No. 1, a left ovarian sample was not obtained. At operation, bilateral follicular cysts with theca luteinization were found. The patient's next menstrual period was 16 days following the catheterization study, suggesting the presence of a preovulatory follicle at the time of catheterization, but the lack of comparative sampling prevents us from making this diagnosis from hormonal data.

In No. 2, DXM suppression results suggested an ovarian etiology of the elevated androgen levels. No samples were obtained from right-sided vessels, but androstenedione output was markedly elevated in both the left ovarian and adrenal vein samples. At laparotomy, wedge biopsy revealed bilateral polycystic ovarian disease.

In No. 7, with primary amenorrhea, elevated plasma corticoids suggested adrenal disease, but urinary free corticoids were consistently normal. Laparotomy was performed because of a large left adnexal mass; bilaterally enlarged polycystic ovaries were discovered, and a mobile right paraovarian cyst was removed.

No. 8, investigated both before and during administration of DXM, had a palpable right adnexal mass prior to the original study. The finding of a threefold elevated testosterone value in the right ovarian vein suggested an ovarian androgen-producing tumor. A laparotomy was performed five months after the second catheterization because of the persistent mass, and bilateral ovarian hyperthecosis with a corpus luteum cyst was discovered. Thus, an androgen-producing tumor was documented in only one patient, No. 5, and the tumor was on the opposite side from that indicated by hormonal studies.

Comment

This study was undertaken to develop a technique whereby excessive hormonal output by the ovary or adrenal might be differentiated and localized. Two catheterization studies were proposed, before and during DXM suppression. Dexamethasone was utilized because of the unusual findings of Stahl and coworkers[4] that increased ovarian androgen production seemed to be rare in their patients. We wished to suppress adrenal androgen production to aid in the differentiation of ovarian disease by identifying ad-

renal hyperfunction. However, two catheterization procedures were not accepted by the majority of patients, and DXM suppression was used when only one study was to be performed. However, as documented by Nos. 10 and 11, reproducibility in obtaining samples was poor, such that the use of DXM did not help in differentiating the site of dysfunction.

Recent reports[1–5] have not addressed the difficulty of the catheterization procedure. Kirschner and Jacobs[1] state that catheterization of both adrenal and both ovarian veins can be performed without undue difficulty in skilled hands and on more than one occasion in a given patient, avoiding the stress of operation and related problems when effluent blood samples are obtained at the time of laparotomy. In contrast, others concluded that adrenal venography had little future because of the difficulty encountered in catheterizing the right adrenal vein.[12, 13] Subsequent investigations have established that catheterization of the adrenal veins may be accomplished, despite the small size of the veins[14] and the considerable variation in anatomic position,[15] and that venography is quite reliable.[16, 17] However, primarily because of the tendency of end-hole catheters to obstruct against the vein wall during aspiration,[18] adrenal venous blood sampling is difficult. Thus, the technique has not proved useful in the diagnosis of Cushing's syndrome.[15]

Gonadal venography has rarely been described. Because of the acute angle between the right gonadal vein and the inferior vena cava, percutaneous jugular catheterization was the primary approach in six of 28 individuals studied by Jacobs.[19] A complete study was achieved 75 per cent of the time, but the right gonadal vein had a double origin in six of 28 patients, and, in 2, it originated from the renal vein. Anastomosis of lumbar vessels and other retroperitoneal veins was documented, suggesting potentially serious admixing of blood in successfully catheterized patients.

Besides the inherent problems of data interpretation from a procedure which accomplishes bilateral sampling less than 80 per cent of the time, one must consider the pattern of glandular output. It has been well documented that cortisol output is episodic.[20, 21] Similar output of androgens by both adrenals has been documented,[26] as illustrated by No. 11 who appeared to have parallel production. When samples were collected from first one and then the other adrenal vein, discordant cortisol values were found; when bilateral simultaneous catheterization was done, concordant values were observed.[22] Thus, variability in base-line cortisol levels, ranging from 5 to 184 μg[18] and 0 to 1700 μg per 100 ml.,[15] is probably due to unpredictable pulsing. Hence, random, nonsimultaneous values are virtually useless. Furthermore, results in No. 11 over 30 minutes suggest that the stress of catheterization itself may provoke cortisol release. Thus, serial sampling is probably required to establish the normal variations in any individual.

Gonadal vein catheterization is no more simple a procedure and has an additional problem. Unlike the adrenals, the ovaries have different steroidogenic capacities, depending upon which is the "active ovary." deJong and colleagues,[23] in Baird's laboratory, using catheterization and isotope-dilution techniques, have conclusively documented a severalfold increase in hormonal output from the ovary containing developing follicles or a corpus luteum.[23] Thus, comparable bilateral steroid values would not be expected, adding to the difficulty in distinguishing ovarian dysfunction.

Finally, the statement by Stahl and co-workers[4] that the procedure is relatively simple, is short in duration, and causes no morbidity cannot be supported and would appear to be an oversimplification. Bayliss and associates[24] have reported a 5 per cent complication rate in 359 cases, including thrombosis of the adrenal or iliac veins, extravasation of the contrast medium, and hematoma formation in or around the adrenal gland. In our study, two of 22 patients were thought to have suffered adrenal hemorrhage or possible infarction as a result of catheterization. During the procedure, both of these individuals developed severe flank pain that persisted, requiring narcotic sedation and analgesia. Increased white blood cell counts and fever were present.

Melby and colleagues,[25] utilizing differential adrenal catheterization for the diagnosis of primary aldosteronism, reported that the procedure took 15 minutes of fluoroscopy time and was accomplished in a two-hour period, with only moderate discomfort. In our No. 2, repeated attempts to enter right-sided veins required over 90 minutes. The total time for the study was never less than 60 minutes and in several individuals required over two hours. Although local anesthesia was utilized, most patients complained of back pain and discomfort from lying still on the radiographic table for fluoroscopy.

Bilateral ovarian and adrenal vein catheterization, although theoretically an attractive means of providing direct information about adrenal and ovarian steroidogenic output, has not proved clinically helpful for several reasons. First, the primary difficulty has been in obtaining and then determining the validity of a sample said to come from a specific vein. Second, the episodic nature of adrenal secretion and the response of the adrenal to stress offer further difficulty in interpretation, and nonsimultaneous sampling from

adrenal veins often provides discordant values. In contrast, dissimilar hormonal output would be expected from the ovaries. Third, the procedure is not benign, and the time and radiation exposure for patients who are of reproductive age are of concern. In summary, bilateral ovarian and adrenal vein catheterization in our hands has not proved clinically helpful in the differentiation of ovarian from adrenal disease or a reliable means of determining the site of ovarian androgen hypersecretion. Consequently, the procedure cannot be recommended in the routine evaluation of hirsute women.

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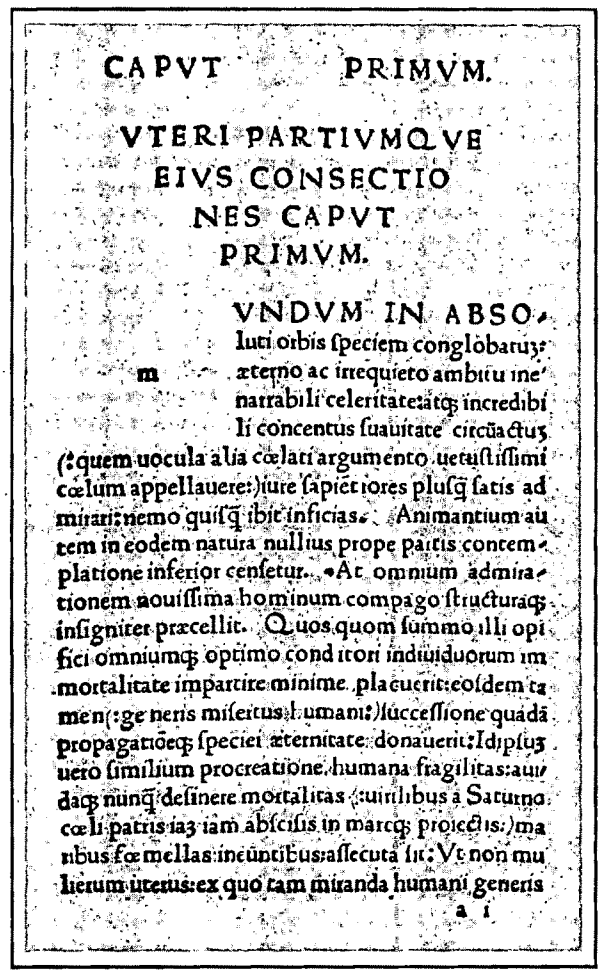
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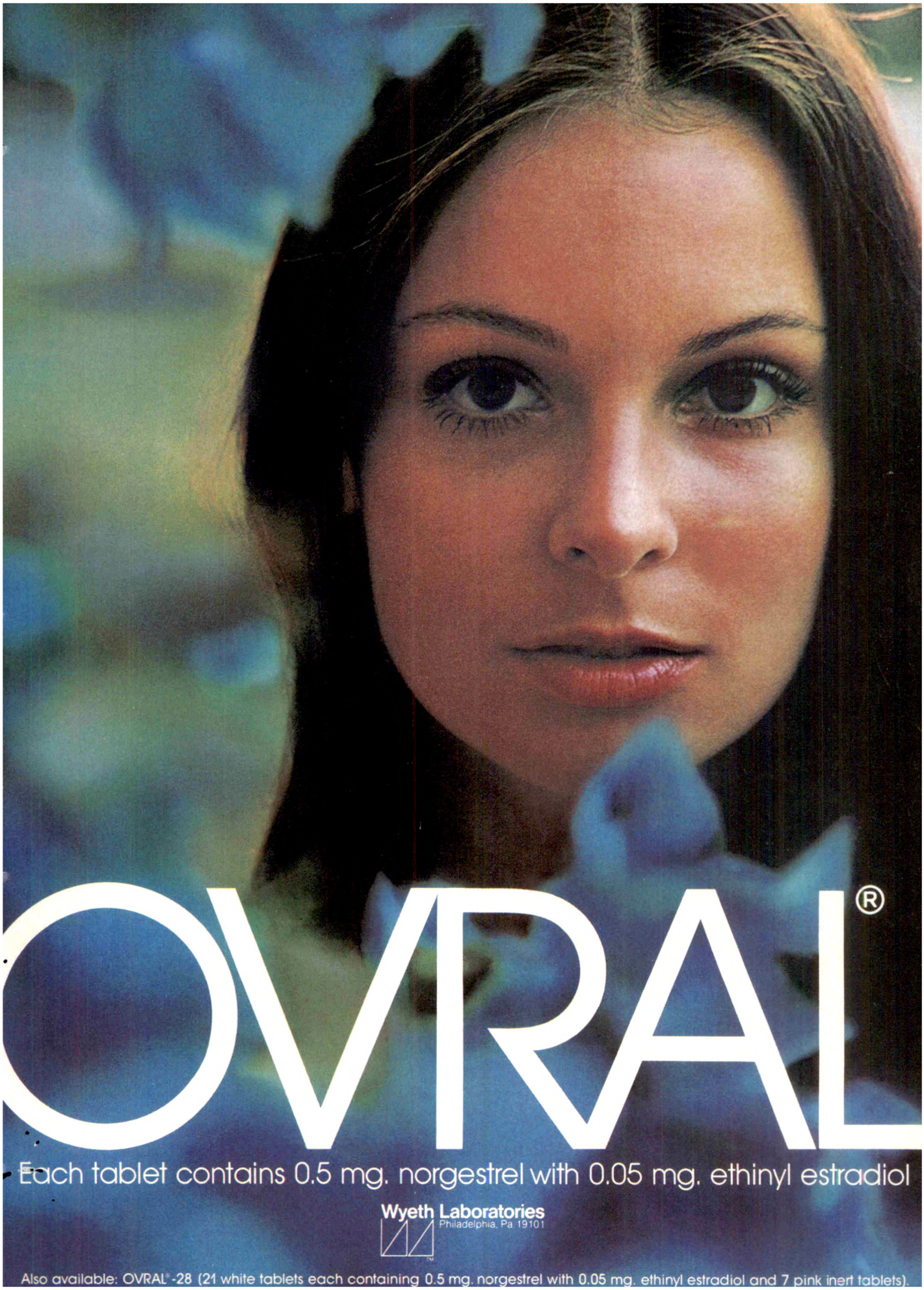
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a i

Bonacciuoli, physician and professor of anatomy at the University of Ferrara, was evidently an outstanding specialist in obstetrics and gynecology. This work, "A Treatise on Women in Nine Parts," formed the basis of his lecture course at the University. It comprised nine chapters, proceeding from a consideration of the anatomy of the female genital tract (see figure at left) to its pathology. He described in detail the mons veneris, the clitoris, and the hymen. He also included a chapter on fetal development with topics such as the means by which the fetus is nourished, at what time fetal movements develop, the soul, and when and by what means it enters the fetus. Other topics considered include: the signs of conception, superfetation, the causes and signs of abortion, the course of pregnancy, delivery and how to ensure a favorable outcome, the puerperium, and care of the newborn infant. Most of the work was derived from Greek and Roman classics. His six-page dedication to Lucrezia Borgia, the duchess of Ferrara, situates the practice of obstetrics at an important Renaissance court. While the original volume is quite rare (only five copies are known), it was reprinted repeatedly over a century and a half.


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Contraindications: In known or suspected carcinoma of the breast (except in cases of progressive disease not amenable to surgery or irradiation, occurring in women at least five years postmenopausal or in men in whom castration is not feasible), in other known or suspected estrogen-dependent neoplasia, thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or in patients with a past history of these conditions, in markedly impaired liver function, and in cases of undiagnosed abnormal genital bleeding.

Warnings: The drug should be withdrawn immediately if there is any evidence of thrombophlebitis, cerebral vascular disorders, pulmonary embolism, retinal thrombosis, proptosis, diplopia, migraine, papilledema, or retinal vascular lesions. Estrogens may be excreted in the mother's milk; the long range effect on the infant has not yet been determined. Hypercalcemia may occur in 15% of breast cancer patients with metastases, indicating progression of bone metastases. If this occurs, estrogen administration should be stopped.

Maternal ingestion of diethylstilbestrol during pregnancy has been associated with the occurrence of vaginal carcinoma in the offspring. Whether this association is applicable to all estrogens is not yet known, but the use of any estrogen in pregnancy is not recommended.

Precautions: Some individuals may exhibit undesirable manifestations of excessive estrogenic stimulation. Estrogens should be used cautiously in patients with epilepsy, migraine, asthma, cardiac or renal disease, or a history of psychic depression. If unexplained or excessive vaginal bleeding occurs, the drug should be discontinued and a thorough investigation made to ascertain that a malignancy is not present.

Pre-existing uterine fibromyomata may increase in size, and patients should be periodically examined. A pre-treatment physical should include a Pap smear and special attention to breast and pelvic organs. These drugs should be used cautiously in women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms. Since continuous use of estrogens will result in prolonged stimulation of the endometrium and breast, estrogens should be administered cyclically.

Estrogens may cause a decrease in glucose tolerance so diabetic patients should be closely observed. These drugs influence the metabolism of calcium and phosphorus and should be used cautiously in patients with metabolic bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Treatment with estrogens may mask the onset of the climacteric. Because they effect epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is not complete.

Prolonged high doses will inhibit anterior pituitary functions, so the drug should be used cautiously in patients in whom fertility is desired.

Urinary stress incontinence may occur in non-pregnant women with large doses. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Certain endocrine and liver function tests may be affected. If such tests are abnormal they should be repeated after the drug has been withheld for two months. Any possible effect of prolonged therapy on pituitary, ovarian, adrenal, hepatic, or uterine function will require further study.

Adverse Reactions: Adverse reactions to estrogen therapy may include: Gastrointestinal: nausea, anorexia, vomiting, abdominal cramps, bloating, cholestatic jaundice, and increase or decrease in body weight. Genitourinary: sodium and water retention, breakthrough bleeding, spotting, and withdrawal bleeding, increased cervical mucus, reactivation of endometriosis, and cystitis-like syndrome. Endocrine: breast swelling and tenderness, possible diminution of lactation when given immediately post partum, increased blood sugar levels, and decreased glucose tolerance. Central Nervous System: headaches, mental depression, increase or decrease of libido, nervousness, dizziness, fatigue, irritability and malaise. Dermatologic-Hypersensitivity: loss of scalp hair, allergic reactions and rashes, hemorrhagic eruption, itching, erythema nodosum, and erythema multiforme. Musculoskeletal: backache. Cardiovascular: an increase in blood pressure in susceptible individuals and aggravation of migraine headaches. Hematologic: A statistically significant association has been demonstrated between the use of estrogen-progestin oral contraceptives and the following serious reactions: thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence suggests an association, the relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuroocular lesions (e.g. retinal thrombosis and optic neuritis). Miscellaneous: Premenstrual-like syndrome and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

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1. Caraway, A. F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A. F. and Vaughn, B. J.: J. Reprod. Med. *10*:171, April 1973.
3. Hayes, O. J.: South. Med. J. *66*:254, Feb. 1973.

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CURRENT DEVELOPMENTS

Gestational and pregestational diabetes: An approach to therapy

JOHN E. TYSON, M.D.
R. ALAN HOCK, B.S.
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The objective of management in the pregnant diabetic patient is to achieve physiologic glucose homeostasis through the use of diet and insulin. As outlined, the numerous ancillary tests developed during the past 15 years to assist the clinician in determining impending fetal death have left much to be desired, especially where metabolic homeostasis has not been achieved prior to the thirty-sixth week of gestation. The statistics from this institution indicate that the maintenance of the plasma glucose concentration below 100 mg. per cent throughout gestation, regardless of the severity of the diabetes, all but removes the risk of maternal-fetal complications due to diabetes. The management is uniform for all patients exhibiting an abnormality of carbohydrate metabolism, and, although it is rather difficult to accept, there have been minimal neonatal complications when the protocol outlined in this presentation has been followed.

DIABETES IN pregnancy would appear ubiquitous since pregnancy itself is acknowledged to be diabetogenic.[1–3] Thus, the diagnosis and treatment of truly abnormal gestational carbohydrate metabolism are difficult. The clinician, whether obstetrician or internist, must display a substantial understanding of the physiology of normal gestation as it pertains to metabolism in order to provide effective therapy.

This communication presents an overview of recent scientific observations regarding the physiology of gestational metabolism and its application to the management of diabetes in pregnancy. Our system of management has successfully reduced the perinatal mortality rate for the combined classes of diabetes in pregnancy at The Johns Hopkins Hospital to 2.3 per cent.*

From the Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine.

Presented in part at the Jubilee Congress of the Medical Association of South Africa, July, 1975.

Reprint requests: Dr. John E. Tyson, Associate Professor, Department of Gynecology and Obstetrics, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

Preamble

Traditionally, the successful management of the gestational diabetic patient has been equated with the delivery of a live infant who survives until at least the sixth postpartum week. We are concerned that this may be an inappropriate end point for assessing the efficacy of prenatal management since we support Churchill and associates[4] who contended that persistent maternal metabolic derangement, measured as ketonuria and hyperglycemia, may be detrimental to the subsequent cerebral development of the child. In more recent studies, Yssing[5] confirmed this impression by observing a positive correlation between subnormal estriol levels in pregnant diabetic patients and subsequent evidence of cerebral damage during a 10 year follow-up. Fifty-

*Based upon a five-year study, July 1, 1969 to June 30, 1974, of 315 patients.

Table I. Classification of pregnant diabetic patients

Joslin Clinic (Boston)			*Rigshospitalet (Copenhagen): prognostically bad signs in pregnancy (PBSP)*	*Johns Hopkins (Baltimore)*
White Class	*Onset*	*Duration*		
A	Pregnancy	Gestation	*Clinical pyelonephritis:* urinary tract infection with an acute elevation of temperature exceeding 39° C., confirmed by culture of the urine	I. *Gestational diabetes* A. Dietary control B. Exogenous insulin and dietary control
B	Over 19 yr. of age	Less than 10 yr.	*Precoma:* diabetic acidosis with a venous standard bicarbonate below 10 mEq./L.	II. *Pregestational diabetes* A. Without related complications
C	10-19 yr. of age	10-19 yr.	*Severe acidosis:* venous standard bicarbonate 10-17 mEq./L.	B. With related com-cations 1. Renovascular 2. Retinal
D	Under 10 yr. of age	More than 20 yr.	*Severe toxemia:* two of the following three signs present: (1) blood pressure > 150/100 for at least five days before delivery, (2) more than 0.1% albuminuria for at least 24 hr. before delivery, (3) severe edema or a weight gain > 20 Kg.	
E	Under 10 yr. of age	More than 20 yr.	*Mild toxemia:* two of the following signs present: (1) blood pressure 140/90 for at least three days before delivery, (2) more than 0.05% albuminuria for at least 24 hr. before delivery, (3) moderate edema or weight gain > 15 Kg.	
F	Under 10 yr. of age	More than 20 yr.	*Neglect:* Failure to follow the recommended regimen, irrespective of the cause, e.g., "psychopathy," low intelligence, first attendance late in pregnancy (at delivery), poor social circumstances, and lack of proper information	
R	Under 10 yr. of age	More than 20 yr.		

one per cent of the progeny of complicated diabetic pregnancies with low 24 hour urinary estriol determinations had considerable cerebral impairment compared to only 22.4 per cent for the group with normal estriol levels ($p < 0.01$). The disorders ranged from cerebral palsy to severe behavioral problems.

We believe that as physicians we must recognize the significance of the maternal plasma glucose concentration in diabetic pregnancy and initiate programs of care designed to restore physiologic glucose homeostasis in the pregnant diabetic patient. Such management virtually eliminates fetal macrosomia and neonatal hypoglycemia, both of which contribute to an increased perinatal mortality rate.

The diabetogenic effect of pregnancy

In normal gestation, the diabetogenic effect of pregnancy is associated with an alteration in the peripheral utilization of glucose[1] and hyperlipidemia,[6] both of which appear secondary to increasing insulin resistance.[3, 7] Such resistance is brought about by contrainsulin factors including estrogen,[8, 9] human growth hormone (HGH),[10, 11] placental lactogen (HPL),[12, 13] and two distinct insulin-degrading enzyme systems in the placenta.[14] That the metabolism of maternal insulin is enhanced by a degradative system was proposed by Freinkel and Goodner[15] as early as 1960. In the intervening years, this sytem has been shown to be maternal in origin in that it resides on the maternal side of the placenta. Gitlin and colleagues showed that insulin fails to cross the placenta in either direction.[16] Thus, the degradation is unilateral.

It is most attractive to propose that the development of gestational diabetes is predicated solely on the pancreatic beta cell inability to maintain suitable insulin secretion in order to support *gestational* glucose homeostasis.[3] Such a hypothesis must also acknowledge the many predisposing factors known to influence insulin secretion,[17, 18] not the least of which is maternal age[19] and obesity.[20] However, it should be noted that appropriate insulin therapy in the pregnant diabetic patient has a favorable effect on pregnancy outcome.[19, 20] It should be emphasized that those investigators reporting a favorable lowering of perinatal mortality rates in diabetic pregnancy of 3.8[21] and 4.7 per cent[22] have guarded closely glucose homeostatic mechanisms by strict dietary and insulin management.

The classification of diabetes in pregnancy

The two most generally accepted classifications of diabetes in pregnancy are those of White[23] and Pedersen and colleagues,[18, 24] shown in Table I. Each is of a predictive value based upon the accumulation of a vast amount of retrospective data. Unfortunately, differences in treatment regimens between the two centers have produced somewhat disparate results in terms of over-all perinatal deaths.[4]

By the White classification, Class A diabetes repre-

sents an abnormality of carbohydrate metabolism appearing during pregnancy and "is treatable" with diet alone. The need for insulin administration in such patients changes the classification immediately. Classes C through F display diverse symptomatology. All such complications adversely influence fetal outcome presumably due to the lack of pregestational diabetic control.

The Pedersen classification evaluates the outcome of diabetic pregnancy under the heading PBSP (prognostically bad signs in pregnancy).[18] Included are those events expected to adversely influence fetal outcome.

Through the application of basic physiologic principles, a more simplified classification has been devised where gestational diabetes is defined as a state of abnormal maternal carbohydrate metabolism beginning at *any* stage of gestation and totally absent by the sixth postpartum week. Gestational diabetes may be controlled by diet or, in the presence of two consecutive basal fasting plasma glucose concentrations in excess of 100 mg. per 100 ml., the addition of exogenous insulin therapy. The term "pregestational diabetes" defines a state of altered carbohydrate metabolism which always antedates the pregnancy. In such cases, the physician must assume the role of surrogate pancreas, providing exogenous insulin according to the patient's metabolic needs as determined by basal and two-hour postprandial glucose concentrations. The route of delivery under optimal conditions is vaginal; however, the detection of fetal macrosomia increases the likelihood of cesarean section. Cesarean section in such cases has reduced the number of birth canal–related trauma which normally increases the rate of infant morbidity and death.[25–28]

Physiology of gestational metabolism

Physiologic alterations in pregnancy metabolism include fasting hypoglycemia and hypoinsulinemia, enhanced ketogenesis,[29] and increased amino acid turnover.[29, 30] Traditionally, such alterations have been ascribed to the decreased peripheral utilization of glucose compensated for by increased glucose transfer to the developing fetoplacental unit.[31] Fasting nonketotic hypoglycemia can be found throughout normal gestation and the immediate puerperium.[32] Fig. 1 demonstrates such basal hypoglycemia and depicts the further decline in the basal plasma glucose concentration as pregnancy progresses. Measurement of the basal plasma glucose concentration prior to breakfast appears to be the single most important factor in terms of identifying alterations in carbohydrate metabolism. Further discussion on this will follow.

Normal basal plasma glucose concentrations lie

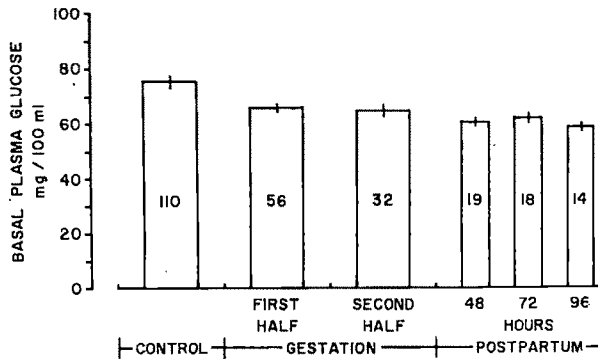


Fig. 1. Fasting plasma glucose concentrations obtained between 7:00 and 8:00 A.M. in healthy, normal pregnant and nonpregnant women. Numbers within the bars represent the total number of patients sampled. A minimum of two basal samples were obtained from each patient and a mean was derived from these.

between 65 and 75 mg. per 100 ml. throughout pregnancy and are somewhat lower (55 to 70 mg. per 100 ml.) in the immediate puerperium.[32, 33] When the glucose/insulin ratio of Perley and Kipnis[34] was applied to our data, a positive rank correlation between the glucose/insulin values in nonpregnant and pregnant women in the first half of gestation was observed ($p < 0.001$), indicating the basal plasma insulin concentration is directly proportional to the basal glucose concentration.

Between the twenty-fourth and twenty-eighth weeks of gestation, placental contrainsulin factors increasingly modify carbohydrate metabolism. This is interpreted as a net antagonism to the action of circulating insulin. The pancreatic response is one of augmented insulin secretion.

For reasons established by screening criteria,[17, 35] pancreatic reserve may be diminished or exhausted, leading to abnormal carbohydrate metabolism (gestational diabetes), the net result of *inadequate* insulin secretion.

The etiology of maternal hypoglycemia during the first half of gestation remains at least partially obscure but may be related to maternal glucose accretion and storage as fat in addition to increased utilization of glucose by the fetoplacental unit.[31] Table II presents the approximate maternal weight increment distribution attributed to pregnancy-related body compartments calculated for isocaloric diets. In the first three months of gestation, the estimated maternal metabolic contribution to fetoplacental growth is minute, yet maternal hypoglycemia and hypoinsulinemia is observed.

A possible explanation for this would be the enhancement of maternal glucose utilization by es-

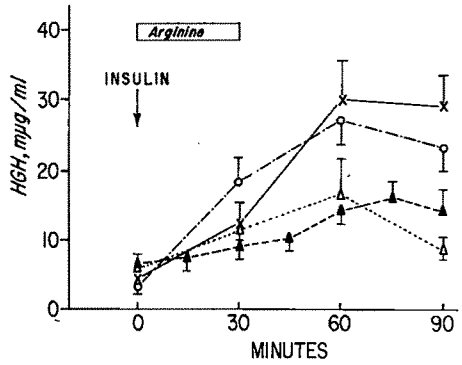


Fig. 2. Plasma HGH responses to the intravenous administration of crystalline insulin (0.1 U. per kilogram of body weight) or the infusion of 30 Gm. of arginine monochloride over a 30 minute interval. Note the significant correlation between HGH responses to both stimuli and the significant difference between control and postpartum patients. X——X, Control insulin; O----O, control after arginine; Δ-----Δ, arginine; ▲———▲, insulin. (Previously published in AM. J. OBSTET. GYNECOL. 103: 313, 1969.)

Table II. Average components of weight gain in pregnancy*

	Cumulative gain (Kg.) at end of each trimester		
	First	*Second*	*Third*
Fetus	Negligible	1.0	3.4
Placenta	Negligible	0.3	0.6
Amniotic fluid (fetal subtotal)	Negligible	0.4 (1.7)	1.0 (5.0)
Increased uterine size	0.3	0.8	1.0
Increased breast size	0.1	0.3	0.5
Increased blood volume	0.3	1.3	1.5
Increased extracellular fluid (maternal subtotal)	0.0 (0.7)	0.0 (2.4)	1.5 (4.5)
Total gain accounted for	0.7	4.1	9.5

*From Pitkin, R. M., et al.: Obstet. Gynecol. 40: 773, 1972.

trogen[8, 36] and the augmentation of insulin's action by progesterone.[9] When the statistics of Hytten and Leitch are compared with those of Pitkin and co-workers,[38] 50 per cent of the total weight gain in the first half of gestation is accounted for by gestationally related changes, including an increase in the plasma blood volume and increases in maternal breast and uterine weight.[38]

A definite sex difference exists in the plasma glucose response to glucose loading and fasting as recently reported by Merimee and Fineberg.[36] This difference may be estrogen-related,[39] and it is more marked during prolonged fasting.[40] Estrogen antagonism to the hyperglycemic effect of pituitary HGH is thought to be partially responsible for this difference[41] and may be mediated via somatomedin (sulfation factor).[43] Estrogen may actually provoke enhanced HGH secretion through a direct action on the pitutiary and hypothalamus,[11, 39] yet it may encourage an increased rate of glucose disappearance.[30]

HGH secretion in early gestation is increased in response to provocative stimuli.[43, 44] Such an increase cannot be rationalized on the basis of cross-reactivity with placental lactogen.[45] In the second half of gestation, HGH secretion is attenuated. Likewise, amino acid infusion and insulin-induced hypoglycemia fail to provoke significant increments in HGH in postpartum women, as shown in Fig. 2. Since the diabetogenic effect of pregnancy is not lessened by the absence of HGH, placental factors, specifically HPL, may replace HGH and continue to antagonize insulin secretion during gestation.[46] Unfortunately, the hypothesis is not clear-cut since HPL is absent from maternal plasma within the first six postpartum hours, while HGH secretion remains attenuated. During this time, maternal hypoglycemia and insulin sensitivity increase markedly. A gradual restoration of pregestational metabolism is observed over the next four to six weeks as pituitary HGH secretion returns.

Plasma glucose measurements in the identification of gestational diabetes

Routine screening for abnormal carbohydrate metabolism has been accomplished with the use of intravenous[47–50] and oral glucose loads.[13, 51] Oral tests have utilized a variety of regimens including an oral 50 Gm. load with blood sampling at one and two hours.[54] O'Sullivan and associates[17] have proved with consistent accuracy the value of such tests in terms of the results of a subsequent three-hour oral glucose tolerance test. Traditionally, however, the three-hour oral glucose tolerance test has provided more accurate information on pancreatic integrity. Such accuracy is related to the provocation of additional insulin secretion by gastric and pancreatic factors such as glucagon and gastrin which are released in response to oral glucose.[55, 56]

The ultimate peripheral maternal plasma glucose concentration observed is directly proportional to the plasma insulin response to a given glucose challenge.[57] While it has not always been possible to measure immunoreactive insulin concentrations along with glucose, such tests are increasingly important in distinguishing various forms of diabetes.[58] Williams[59] has emphasized that the insulin responses to glucose ingestion are related to: (1) the insulin level following an overnight fast; (2) the insulin increment within the first few minutes following glucose ingestion; and (3) the insulin level two to three hours after glucose intake. In normal gestation, insulin levels correlate with the

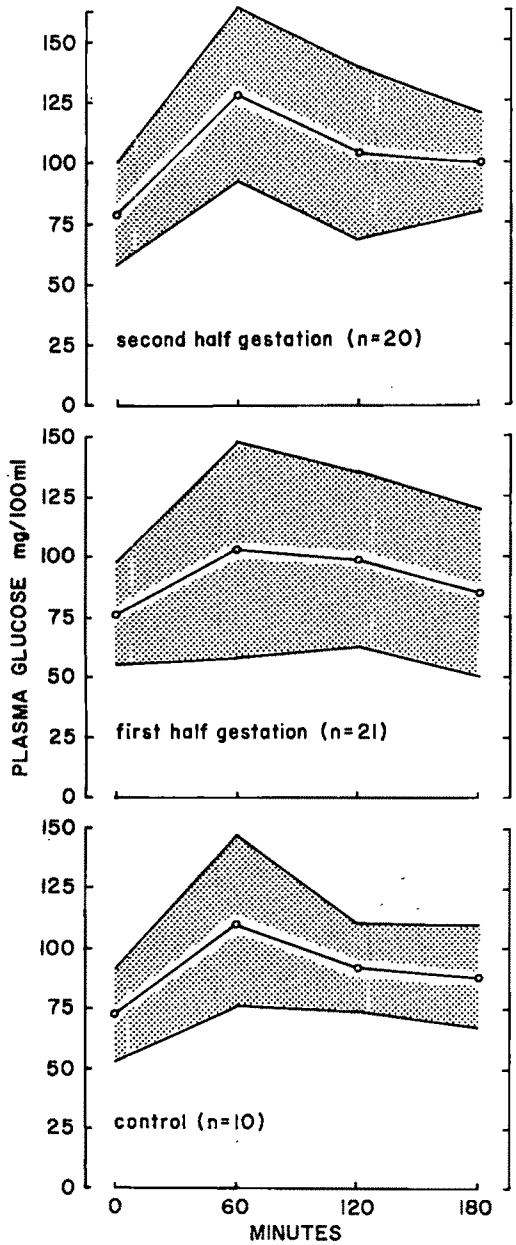


Fig. 3. Plasma glucose concentrations in healthy women following the ingestion of 100 Gm. of glucose. The shaded areas represent two standard deviations from the mean.

basal plasma glucose concentration and are lower in earlier gestation than at term.[31]

The maintenance of normal glucose tolerance during gestation occurs at the expense of exaggerated insulin secretion. Yen and colleagues[60] have suggested that the retardation of glucose deposition in pregnancy is associated with an increased glucose pool as well as a defect in the timing, quantity, and quality of the insulin response to intravenous glucose. These physiologic observations incriminate the effect of contrainsulin

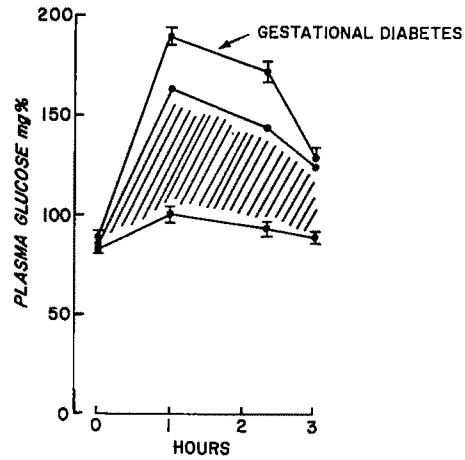


Fig. 4. Plasma glucose concentrations in 84 women with gestational diabetes after the oral ingestion of 100 Gm. of glucose. These values are compared to the mean glucose concentrations observed in 50 normal pregnant women who underwent an oral glucose tolerance test between the twentieth and twenty-fourth weeks of gestation. The shaded area represents the difference between the normal values and the upper limits of normal commonly used to define the range of normal glucose tolerance.[17]

factors (see below). Since the maintenance of gestational euglycemia occurs at the expense of altered insulin secretion, the physician must develop strict standards for evaluating carbohydrate metabolism in pregnancy as well as new objectives for management.

Plasma glucose concentrations following the ingestion of 100 Gm. of oral glucose are shown for normal women in the first and second halves of gestation (Fig. 3). The mean glucose concentration in the first half of gestation at one hour was 103.1 ± 5.2 mg. per 100 ml. compared to a one-hour plasma glucose concentration of 128.3 ± 4.4 mg. per 100 ml. in the second half of gestation. These values compare favorably with those of studies reported by others[17] and are consistent with findings in our prepregnant control subjects.

The standard error of the mean of such values was unusually small. Nevertheless, each point was calculated to include two standard deviations from the mean to establish 95 per cent confidence limits for the testing procedure.[61] As an indication of the abnormality in carbohydrate metabolism observed in women in our clinic, Fig. 4 presents the mean curve for abnormal glucose tolerance in 84 women with gestational diabetes. Mean maternal weight was 165 ± 13 pounds or >20 per cent of ideal body weight.* While the abnormality was grossly apparent in these women, care should be taken to evaluate the glucose curve obtained

*Metropolitan Life Tables, 1959.

in 50 normal healthy pregnant women between the twentieth and twenty-fourth weeks of gestation. The single middle line demarcates what traditionally has been the upper limit of normal for glucose testing.[17] Since the physiologic response to oral glucose is much lower, women with such abnormalities may escape detection on testing but are usually identified post partum, having been delivered of infants weighing >4,000 gram.[62, 63] In our clinic, 9 per cent of all women screened for diabetes on the basis of existing criteria have negative glucose tolerance tests yet deliver infants weighing >4,000 grams.[64]

Since the maximal diabetogenic effect of pregnancy is observed beyond the twenty-fourth week of gestation, it has been customary to retest all women with prior negative glucose tolerance tests between the twenty-eighth and thirty-second weeks of gestation. Eighty per cent of such repeat tests are positive.

Diabetic management based upon the plasma glucose concentration

Our screening criteria of the potential gestational diabetic patient have been reported elsewhere.[31] The three-hour oral glucose tolerance test is used as a matter of preferance, although the 50 Gm. test is both practical and accurate.[17, 52] Tests are performed on all women fulfilling two or more of the criteria at the time of registration for prenatal care. Routine screening of all pregnant women has been suggested but is currently impractical in our clinic due to staff limitations.

The identification of an abnormal glucose tolerance test is followed by the use of the *glucose panel* or profile which consists of regular blood sampling every two hours over a 14 hour period in order to evaluate not only the *degree* of abnormality but also the *timing* of the abnormal glucose values. Diurnal fluctuations are also recorded. Interpretation of the results is made with allowance for the normal diurnal fluctuation in the plasma glucose concentration.[65, 66] The patient's diet, activity, and/or insulin requirement are now adjusted separately according to the glucose panel. Subsequent profiles are obtained at appropriate intervals to confirm the degree of control.

To avoid the need for persistent blood letting, an alternate method of plasma glucose testing has been sought. It is our belief that, to be managed correctly, pregnant diabetic patients must have determination of basal glucose levels. This was accomplished through the use of glucose oxidase–impregnated paper sticks* where capillary *blood* glucose concentrations were obtained each morning. Women were instructed to obtain blood from the lateral aspect of a terminal digital phalanx with a sharp stylet. Samples were obtained each morning prior to breakfast or insulin administration. The colorimetric reading thought to be most sensitive to the naked eye lies between 45 and 90 mg. per 100 ml. or well within the range considered to represent "adequate chemical control." Twelve women have successfully completed pregnancies where *daily* glucose values were obtained by this method. The economy associated with the determination of the blood glucose concentration by this method appears to justify its use. In each instance, an infant whose weight was within the range of infants born to normal mothers at the comparable stage of gestation was delivered.

The accuracy of Dextrostix has been studied by Spellacy and co-workers[67] utilizing a reflectance meter. The addition of this instrument greatly enhances the accuracy of our results. Due to subtle color changes between varying concentrations of blood glucose, the glucose oxidase–impregnated stick is of little value at the extremes of blood sugar determination, that is, below 25 mg. per 100 ml. and above 175 mg. per 100 ml. Since the objective of our management was to maintain the blood glucose concentration between 45 and 90 mg. per 100 ml., the efficiency of the method was adequate.

Daily caloric management

Marked differences in dietary intake exist between women of various socioeconomic classes. The normal clinic population at Johns Hopkins is 20 per cent over ideal body weight due to a dietary intake rich in carbohydrate. Women of a higher socioeconomic class, on the other hand, are usually <5 per cent over ideal body weight because they utilize a more stable diet. It has been suggested that the optimal maternal weight gain should be 10 to 12 kg.,[38] requiring an additional 27,000 kilocalories for the pregnancy or an additional intake of 300 calories per day. The energy requirements of the pregnant diabetic patient appear to differ from those of the prediabetic person, but this may be related to the degree of obesity in the study population.[68]

In our clinic, diet is normally restricted initially to 1,800 calories per day, divided into at least 100 Gm. of protein, 200 Gm. of carbohydrate, and the remainder fat. The arbitrary choice of 1,800 calories was to allow for regular adjustments in the form of increments or decrements of 200 calories per day, based upon the appearance of ketonuria.

Immediately following the identification of abnormal carbohydrate metabolism, women are admitted to

*Dextrostix, Ames Co., Inc., Div. Miles Labs., Inc., 819 McNaughton Ave., Elkhart, Indiana 46514.

the hospital for three days, during which time the glucose profile is established and daily calorie counts are instituted. During the first hospital day, the patient ingests a diet of choice which is occasionally found to be equivalent to less than 1,200 calories per day and accompanied by morning acetonuria. At that time, a nutritionist instructs the patient in proper diet. A few authors advocate the use of elaborate formulas to provide for weight reduction in pregnancies complicated by maternal obesity.[69] However, it is our belief that such metabolic attrition may be detrimental to fetal growth and development since it is known that caloric restriction in pregnant animals is associated with maternal weight loss and a reduction in litter size, as well as an increased incidence of fetal abnormalities and deficiencies in intellectual function.[70]

On our regimen, maintenance of a maternal weight gain of about 0.25 pounds per week without acetonuria has been accomplished. In 53 women with gestational diabetes, careful dietary management was applied between the initial visit at 20 to 24 weeks until term. Fig. 5 compares their weight gain with that observed in 20 healthy pregnant women of comparable age who ate freely during the same time period. The mean birth weight of infants born to both groups was comparable for the stage of gestation at which delivery occurred.

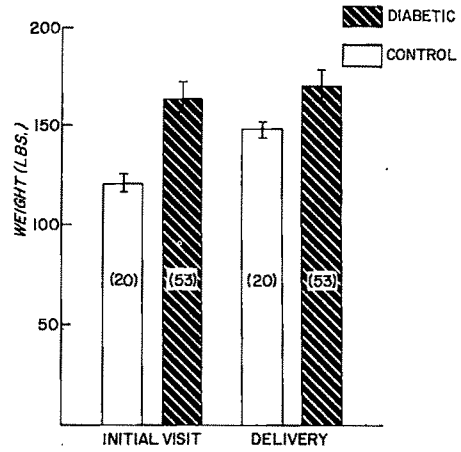


Fig. 5. The mean weight of 53 gestational diabetic patients and 20 nondiabetic women matched according to the date of registration for prenatal care and compared by weights at the time of delivery.

Evaluation of the fetoplacental unit

Until viability, tests of intrauterine fetal welfare in diabetes add little to management. Therefore, 24 hour urinary estriol excretion is deemed to be of prime importance in determining fetal well-being in the pregnant diabetic patient.[71–75] However, not all investigators have found them to be of significant value.[76–78] Greene and Beargie[70] reported a marked improvement in perinatal salvage when 24 hour urinary estriol excretion exceeded 4.0 mg. High estriol concentrations can precede intrapartum fetal distress and are associated with increased fetal wastage.[76] However, alterations in urinary estriol excretion may be predicated on an alteration in fetal adrenal function, especially in the pregnant diabetic patient[30–82] where altered fetal adrenal function may accompany persistent fetomaternal hyperglycemia.

The positive correlation between urinary estriol excretion and fetal weight suggests that in the presence of a gross elevation in estriol a large fetoplacental unit might exist within a poorly controlled pregnant diabetic patient.[82, 83] On the contrary, low estriol levels may persist in a well-controlled pregnant diabetic patient who has evidence of severe renal impairment.[84]

In a study of 159 pregnant diabetic patients with White classification B to D, Klebe and associates[78] reported an enhanced urinary excretion of estriol in the last trimester of pregnancy which they believed was related to the poor degree of diabetic control. They also concluded that a curve of urinary estriol excretion in patients with well-controlled diabetes should be used as the control for more complicated diabetic pregnancies since urinary estriol excretion in patients with well-controlled gestational diabetes parallels the results obtained in patients with normal pregnancy.

Results of a study by Samaan and co-workers[28] suggest that regardless of the class of diabetes the identification of a low urinary estriol excretion is not always associated with a successful or unsuccessful fetal outcome. A 50 per cent infant mortality rate was encountered during attempts at operative delivery. In our experience, urinary estriol determinations are of value when performed daily, a theory previously advanced by others.[75] However, it is important to realize that estriol levels should not be used as a single determinant of fetal well-being.

Placental lactogen (HPL) and diabetic pregnancy

A product of the syncytiotrophoblast, HPL synthesis and secretion are directly proportional to placental size and weight.[45, 85] HPL is found in the peripheral plasma in increasing concentrations throughout pregnancy and has been used by some investigators as a prognostic index of impending intrapartum fetal distress.[59, 86–88] The significance of plasma HPL concentrations in diabetic pregnancy has been questioned since high levels are inevitably found in pregnant patients with poorly controlled diabetes.[13, 85, 89–91] We have alluded

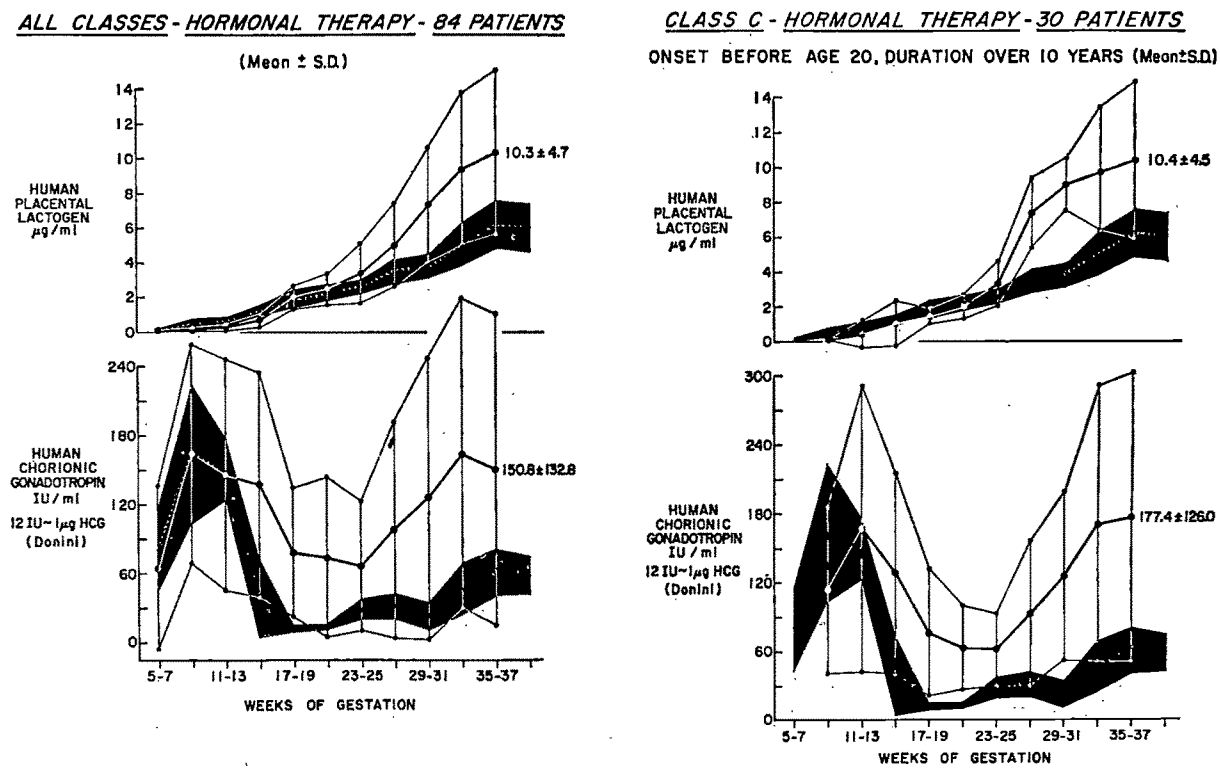


Fig. 6. Left, Placental lactogen and chorionic gonadotropin concentrations in 84 women who had diabetes in pregnancy. All values are mean ± the standard deviation. Right, Corrected data for HPL and HCG in 30 of the 84 patients who had Class C diabetes. The elevated mean HPL concentrations indicate placental size and, by analogy, the degree of diabetic control which must have existed.

previously to the questionable role of HPL determinations in the management of the pregnant diabetic patient. However, HPL may be an etiologic factor in the frequency of ketoacidosis in late gestation.[91]

Placental growth is dependent upon fetal growth.[92] Fetal growth appears to be in some way dependent on the concentration of maternal substrates traversing the placenta, principally glucose. With persistent maternal hyperglycemia, fetal and placental macrosomia results.[93–95] When fetoplacental macrosomia exists, the HPL concentration is elevated and, therefore, seems a more accurate indicator of the *lack* of diabetic control. Fig. 6 presents data on 84 diabetic patients from The Joslin Clinic. Serum HPL was elevated well beyond two standard deviations of the mean obtained from a series of normal pregnancies.[87] Even with correction for the class of diabetes, a significant alteration in the mean HPL concentration was not observed. Under such circumstances, one would expect the pregnancies to be in jeopardy.

Elevated HPL concentrations may influence maternal metabolism, and such influence may be exaggerated where the HPL concentration is elevated, as in the case of the patient with uncontrolled diabetes.[87] Evidence supporting the role of HPL as a physiologic glucose antagonist can be observed in the results of glucose tolerance tests obtained in presumably normal women carrying twins between the thirtieth and thirty-second weeks of gestation.[32] The mean plasma HPL concentration in these women was 6.2 μg per milliliter compared to 3.8 μg per milliliter in the plasma of 21 normal pregnant women of comparable gestational age.

HPL enhances insulin secretion directly.[96] A further indirect stimulation of pancreatic function is brought about by HPL through its antagonism of peripheral glucose utilization.[46] The basal hypoinsulinemia accompanying high HPL concentrations can be seen in the mean plasma insulin concentrations for twin pregnancies shown in Fig. 7. Here, augmented insulin secretion followed an oral glucose load yet failed to maintain normoglycemia. As a result, the following hypothesis is proposed. In the presence of uncontrolled gestational diabetes, maternal hyperglycemia promotes fetoplacental macrosomia. This, in turn, facilitates placental growth, leading to an elevated plasma HPL concentration which provides for an increased challenge to maternal metabolic homeostasis. The net result is a worsening of the diabetic condition.

The presence of a decrease in an already elevated

HPL concentration in a pregnant patient with poorly controlled diabetes is considered to be of real significance yet may not be identified early enough to assist the physician in deciding the outcome of the pregnancy. Although our concept may be disputed,[97, 99] others strongly support the belief that plasma HPL determinations are of use only in the detection of imminent abortion.[100, 101] As with HPL determinations, the measurement of heat-stable alkaline phosphatase is of limited value in diabetic pregnancy.[102]

Sonography

While exaggerated linear growth is the hallmark of infants delivered to patients with poorly controlled diabetes, the fetal head size as measured by the biparietal diameter is similar to that obtained from infants of normal pregnancies at a comparable stage of gestation up to 27 weeks.[103] Beyond this, the biparietal diameter is significantly greater in the patient with poorly controlled gestational diabetes. The use of sonography in our clinic has confirmed a normal growth pattern of the fetal skull prior to viability and is, therefore, used to assess fetal age and maturity. Fetal head mensuration is not used as a determinant for the route of delivery since it would appear to bear no relation to the width of the shoulders and the circumference of the fetal trunk, two measurements which appear critical to a successful atraumatic vaginal delivery. Without adequate maternal metabolic control, fetal macrosomia in a woman with an otherwise normal gynecoid pelvis will usually produce shoulder dystocia.[22, 28] It is this dystocia which accounts for the increased infant morbidity associated with vaginal delivery.[27]

The prognostic significance of amniotic fluid parameters

Amniotic fluid glucose (AFG) is elevated in diabetic pregnancies.[104] However, a careful evaluation of these data indicated that this may be related to the maternal glucose concentration since the mean fasting plasma glucose concentration in the diabetic group was 134.3 ± 11 mg. per 100 ml. compared to 86.1 ± 9.0 mg. per 100 ml. in control subjects. AFG has also been shown to be higher in pregnancies where infants suffer from subsequent neonatal hypoglycemia.[105] Elevated AFG implies a lack of precise maternal metabolic control. Amniotic fluid creatinine levels are useful in determining fetal maturity.[106] Pitkin and Zwirek[106] found a positive correlation between amniotic fluid creatinine greater than 2.0 mg. and maturity greater than 37 weeks. Unfortunately, this is of little value in the patient with severe diabetes where delivery occurs prior to 35 weeks.

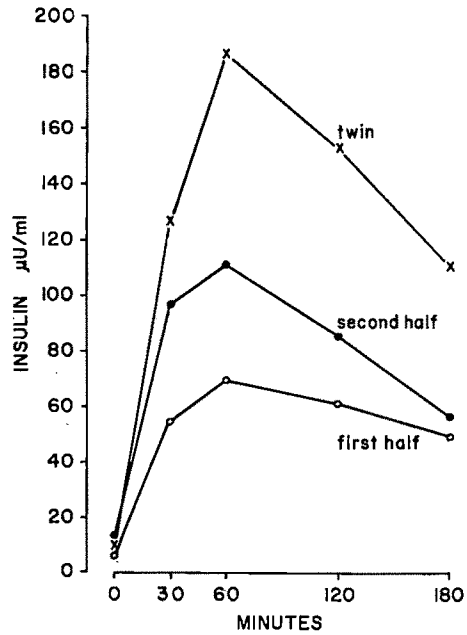


Fig. 7. Mean insulin concentrations following the oral administration of 100 Gm. of glucose to 21 women in the first half of gestation and 20 women in the second half of gestation as compared to the insulin response observed in eight women carrying twins who also ingested 100 Gm. of glucose between the thirty-second and thirty-fourth weeks of gestation. While basal insulin concentrations in the two normal groups were comparable, an exaggerated insulin response was observed in women carrying twins.

Oxytocin challenge test

Recently, emphasis has shifted toward the use of antepartum fetal monitoring during spontaneous or induced uterine contractions as a means of detecting impending fetal compromise. The oxytocin challenge test (OCT) has been used in this manner and may be of value in the management of the pregnant diabetic.[107]

The monitoring of three spontaneous uterine contractions 40 to 60 seconds in length over a 10 minute interval is considered adequate for performing the test. However, induction of contractions with intravenous oxytocin may be performed after the thirtieth week of gestation when no spontaneous contractions are present. In a study of pregnant diabetic patients with a previous history of stillbirth, Freeman[107] found the OCT's at 34 weeks and thereafter are positive when a decline in the plasma estriol is observed or *immediately* prior to intrauterine fetal death. The following case presentation emphasizes this point.

Case management evaluation No. 1

A 25-year-old, white, diabetic primigravid woman was admitted for evaluation at Week $33^{5}/_{7}$ of gestation. She was a juvenile diabetic and weighed 107 pounds. Diabetic control prior to admission had been

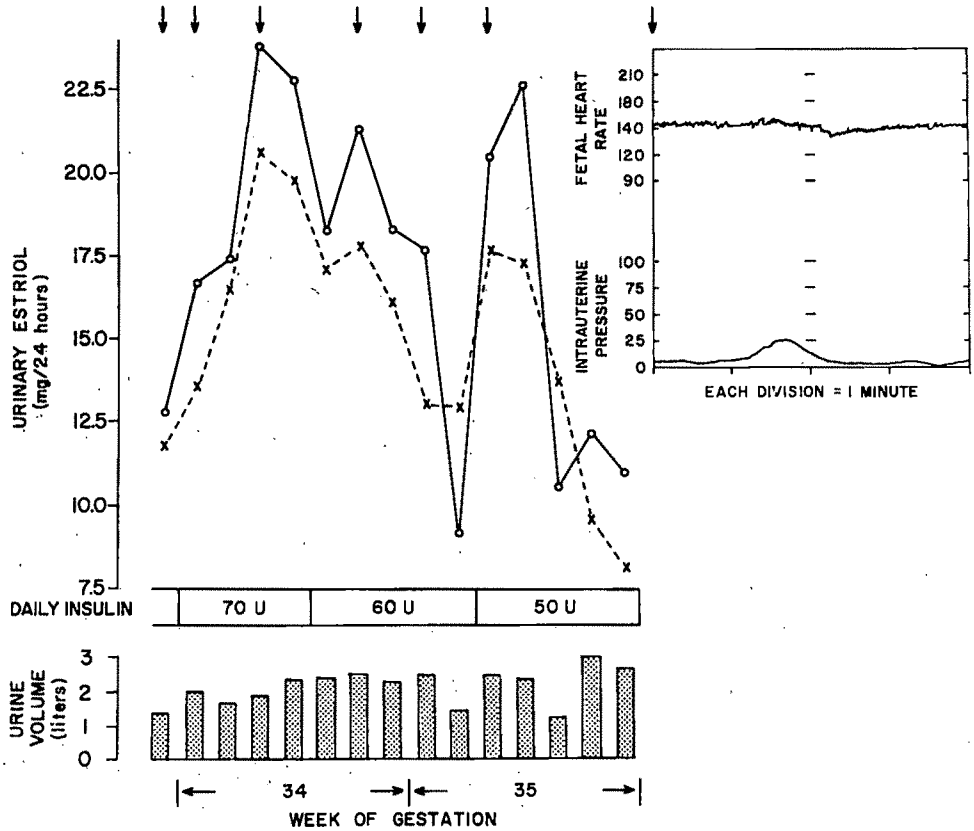


Fig. 8. Twenty-four hour urinary estriol values (o——o) and estriol/creatinine concentrations (x---x) in a patient with pregestational diabetes. ↓ Indicates the use of an OCT. The eighth OCT which was performed immediately prior to abdominal delivery is shown in the inset. A late deceleration pattern in the fetal heart is evident.

fair although fasting blood glucose values ranged above 200 mg per cent on several occasions. Mild pre-eclampsia was evident, and urinary estriol excretion was low.

Fig. 8 summarizes management from admission until delivery. During the thirty-fourth week of gestation, 24 hour estriol excretion rose. For five additional days, estriol values fell, accompanied by increased insulin sensitivity and hypoglycemia. Repeat OCT's were negative.

The first decline in urinary estriol excretion was thought to be related to an inadequate 24 hour urine collection. Therefore, intervention was postponed. Five days later, after estriol had risen again followed by a fall, a decision was made to intervene with operative delivery. OCT's performed throughout the hospital stay were negative except for one performed immediately prior to the cesarean section which demonstrated late deceleration in the fetal heart rate.

Amniocentesis revealed a lecithin/sphingomyelin (L/S) ratio of 1.27; creatinine was 2.4 mg. per cent. A 2,840 gram male infant with an Apgar score of 1 was delivered. The fetal arterial blood pH was 7.19 with a Po_2 of 24 mm. Hg. Pco_2 was 61 mm. Hg. The neonate was treated for 10 days in the intensive care nursery for refractory hypoglycemia.

In retrospect, failure to acknowledge the falling insulin requirement as significant was wrong. The clinician had awaited a repeated fall in estriol before considering delivery. There was adequate evidence for borderline maternal metabolic control prior to hospital admission which, no doubt, contributed to the fetal compromise observed at 34 weeks. On the other hand, little import was placed on erratic estriol determinations in the presence of repeated normal OCT's. The OCT was positive presumably when the infant was in a most severe state of metabolic acidosis. The emergency conditions under which cesarean section was performed intensified the degree of subsequent fetal morbidity.

Fetal macrosomia

While the accurate estimation of intrauterine fetal size by external abdominal palpation is difficult, the identification of fetal macrosomia by this means is

of prognostic significance in terms of the route of delivery. In poorly controlled diabetes, carbohydrates are utilized by both mother and fetus while fat storage by the fetus is enhanced presumably in response to fetal hyperinsulinism. Thus, fetal macrosomia appears to be the direct result of maternal hyperglycemia.[108]

This concept was recently challenged when Szabo and Szabo[109] proposed that glucose is not the major precursor of triglyceride fatty acids but a primary substrate for α-glycerophosphate which, in turn, allows free fatty acid (FFA) esterification. Citing numerous authors, they suggested that insulin treatment in pregnant diabetic patients lowers maternal FFA levels by blocking lipolysis. Gillman[110] had produced evidence that would seem to refute this hypothesis. Following the diurnal fluctuation in plasma glucose and FFA in normal and diabetic women, he showed that insulin therapy had no significant effect in maternal FFA levels. Rather, the plasma glucose concentrations *alone* were affected. The hypertriglyceridemia of pregnancy was correlated more fully with the maternal HPL concentrations. Fetal size correlated positively with maternal glucose, not FFA.

It would seem that hyperinsulinemia accompanies increased fetal fat deposition.[93, 95, 111] Emerson and associates[68] concluded that the total energy expenditure in diabetic pregnancy was greater than that of a group of pregnant control subjects. However, no account was taken of the degree of maternal obesity associated with the diabetes. In our experience, obesity complicating diabetes greatly enhances the risk of fetal macrosomia, even in the presence of normoglycemia. Stallone and Ziel[27] observed 8 per cent perinatal morbidity secondary to birth trauma following vaginal delivery of infants of diabetic mothers. The well-known bone and nerve injuries which accompany such deliveries led them to conclude that cesarean section was the delivery method of choice in infants estimated to weigh more than 9 pounds. In a careful analysis of data related to fetal size, the hypothesis is confirmed, not only in terms of intrapartum fetal distress and trauma but also as far as the risk of unexplained stillbirth and neonatal complications is concerned.[26, 28, 112–116] The following case report provides an illustration of the risks associated with fetal macrosomia and vaginal delivery.

Case management evaluation No. 2

A 23-year-old woman, gravida 2, para 1, was referred for emergency management in the thirty-seventh week of gestation. Fifteen months previously, she had been delivered vaginally of a male infant weighing 4,649 grams. Shoulder dystocia resulted in persistent brachial plexus paralysis. While an abnormal oral glucose tolerance test had been obtained in the first pregnancy at 28 weeks, no specific dietary management had been prescribed. In addition, the patient had suffered a rectovaginal fistula during the first delivery.



Fig. 9. Buddha-like appearance of a 5,046 gram infant born to a woman with poorly controlled gestational diabetes.

A glucose tolerance test in the thirty-fifth week of gestation of the current pregnancy revealed a fasting blood glucose concentration of 254 mg. per cent. The patient was counseled on diet, yet insulin therapy was not ordered. In the thirty-seventh week of gestation, she was considered for delivery. The cervix was soft and 50 per cent effaced. The sonogram indicated a biparietal diameter of 8.7 cm. The fundal height was estimated to be 42 cm. Cesarean section was performed for a 5,046 gram male infant who suffered severe neonatal hypoglycemia and transient bouts of apnea. Fig. 9 presents the classic signs of uncontrolled maternal diabetes in this child.

While the outcome of the pregnancy was satisfactory, the case management raises several important questions, not the least of which was the identification of abnormal carbohydrate metabolism in the first pregnancy without the implementation of appropriate

metabolic care. While the fetal hazards of vaginal delivery have been described, maternal morbidity associated with cesarean section in the woman with great obesity is also considered.[117] Judgement would seem to indicate that cesarean section is the delivery route of choice when macrosomia is present. Moreover, neonatal hypoglycemia must be expected when persistent maternal hyperglycemia is suspected.[22, 118]

Diabetic retinopathy

Fetal outcome in maternal diabetes complicated by retinopathy is poor.[23, 119, 120] Retinopathy is a common finding in patients with poorly controlled diabetes of a long duration. A more fulminating form of retinopathy is associated with neovascularization of the vitreous humor. While its course in pregnancy is poorly defined,[121] hypophysectomy has been performed during pregnancy when vision was severely impaired.[122] The estimated incidence of retinopathy in pregnant diabetic women is 25 per cent.[121] The majority, probably 80 to 90 per cent of these patients, have background changes. The remainder display the more advanced, proliferative type.

The effect of pregnancy on diabetic retinopathy is unknown although clinical impression suggests that background retinopathy is relatively unaffected, while proliferative changes tend to worsen.[23, 123] The risk of developing diabetic retinopathy de novo in pregnancy has not been determined. It has been our custom to perform a complete visual assessment of all insulin-dependent diabetic patients at the time of registration for prenatal care. Repeat examinations are performed immediately prior to delivery and again at 6 weeks post partum.

Oral hypoglycemic agents and diabetes in pregnancy

Oral hypoglycemic agents have been prescribed in pregnancy.[115, 125] Unfortunately, their low molecular weight provides for placental transfer and a possible effect on the fetal pancreatic islets.[124] Many oral hypoglycemic agents either enhance pancreatic insulin secretion or modify its peripheral action. It is incumbent upon the physician to weigh the possible benefits of using these drugs against the possible hazards. The use of such medications in patients with gestational diabetes even when the disease is secondary to obesity might provoke complete pancreatic exhaustion leading to dependence on exogenous insulin. As a practical measure, and due to evidence that some agents may increase cardiovascular complications, oral hypoglycemic agents are not prescribed in our clinic. Moreover, placental transfer of such agents may actually promote fetal pancreatic hyperplasia and promote abnormalities of neonatal carbohydrate metabolism.

Timing and mode of delivery

Attention must be paid to maintaining physiologic antepartum normoglycemia to ensure that delivery in the gestational and pregestational diabetic patient is performed as near term as possible.[19, 20, 118] The maintenance of a fetal size and head circumference consistent with normal gestation greatly influences the perinatal mortality rate in favor of increased fetal survival regardless of the route of delivery.

Since the factors influencing unexplained intrauterine stillbirth in the pregnant diabetic patient are as yet poorly defined, we have had to make several empiric decisions based upon our ability to ensure that a pregnant diabetic patient will reach the latter part of the last trimester of pregnancy in a sound metabolic condition. Therefore, we have chosen to deliver infants of all gestational and pregestational diabetic patients between the thirty-sixth and thirty-eighth weeks of gestation. The objective of management is to provide for a timed, controlled delivery. This delivery, whether vaginal or abdominal, is performed during the early morning hours.

When the decision to deliver has been made, based upon an evaluation of all the parameters previously described, cervical inspection is performed on the evening before the designated date of delivery. It is important to point out that if amniocentesis is performed it is not performed with the idea of postponing the day of delivery should the parameters indicate a premature infant but merely to inform the pediatrician of the approximate gestational age of the infant he or she is about to receive.

Induction of labor with oxytocin is undertaken if the cervix is at least 50 per cent effaced and soft with 2 to 3 cm. of dilatation. A six to eight hour induction is begun, and failure to detect further cervical dilatation and descent of the fetal head within the six-hour interval prompts us to perform an immediate cesarean section. Obviously, the presence of fetal malpresentation or an unfavorable cervix results in immediate cesarean section. The approach just outlined is applied only to gestational diabetic patients whether controlled with diet or diet and insulin. It has been our empiric decision to deliver all pregestational diabetic patients by cesarean section.

Insulin management during gestation

We have utilized isophane (NPH) insulin combined with the more short-acting crystalline zinc insulin as a

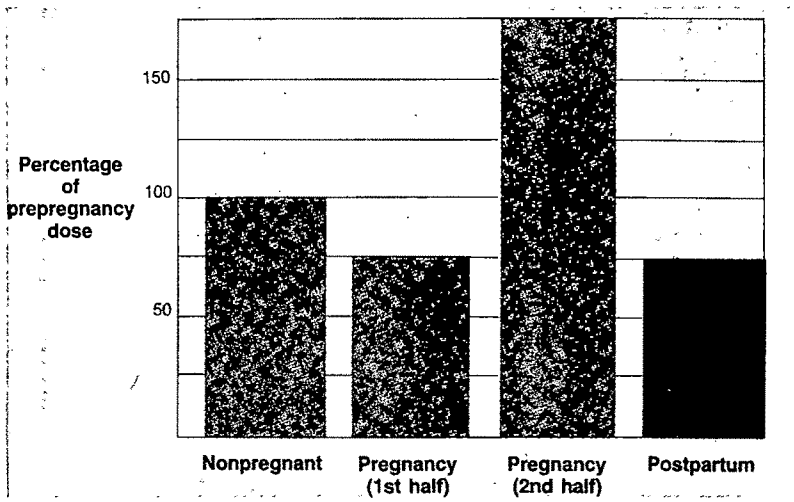


Fig. 10. Diabetic insulin requirements related to pregnancy. The diabetic patient's need for insulin is sharply reduced during the first half of pregnancy because maternal glucose is transferred to the fetus and because food intake is ordinarily diminished from nausea and vomiting. During the second half of pregnancy, insulin requirements increase even more sharply, to about 167 per cent of the prepregnant dose. This increased need for insulin results from the antagonistic action to insulin of the rising concentration of placental hormones. After delivery, the loss of these placental hormones and the continued suppression of growth hormone secretion bring the over-all maternal insulin requirement down to about 67 per cent of the usual prepregnant dose. Insulin requirements gradually increase during the postpartum period, usually reaching the prepregnant level six weeks after delivery. (Adapted from a chart by Tyson, J. E., and Felig, P.: Medical aspects of diabetics in pregnancy and the diabetogenic effects of oral contraceptives, Med. Clin. North Am. 55: 953, 1971. Reprinted from Patient Care 9: 109, 1975.)

regimen of choice. Fig. 10 shows changing insulin needs in pregnancy. The daily dosage may be split into two injections, one in the morning and the other in the evening, based upon the results of the plasma glucose profile. Significant increases in maternal insulin requirement are anticipated beyond the twenty-fourth week of gestation. The increasing insulin requirement at this stage of gestation is so consistent that it leads us to believe it represents another diagnostic parameter when attempting to determine the exact stage of gestation.

As mentioned previously, in gestational diabetes, a basal plasma glucose concentration of greater than 100 mg. per 100 ml. on two consecutive occasions with the patient under strict control is an absolute indication for the addition of insulin to the patient's management.

Insulin therapy during delivery

Insulin is withheld on the designated day of delivery. Fifty grams of glucose is administered as a 5 per cent solution during a four to six-hour period. Severe hyperglycemia or glucosuria is never encountered under these circumstances.

The most critical time for precise metabolic management is following delivery. Therefore, we have adopted a system of maintaining maternal glucose homeostasis with the use of intravenous insulin and glucose only. The blood glucose concentration is monitored at hourly intervals by microtechniques and semimicrotechniques. All research studies have been performed on *plasma* while clinical management of the patients is based upon the *blood* glucose concentration, the difference between plasma and blood glucose determinations being approximately 14 per cent.

The administration of insulin post partum is by slow intravenous drip with a constant-infusion apparatus. Crystalline zinc insulin (20 to 25 U.) is added to a 100 ml. bottle of physiologic saline to which a small amount of the patient's blood previously has been added to provide a coating of protein in the bottle in order to reduce the degree of insulin adsorption to glass.

With a half life of 15 to 17 minutes,[59] insulin is active at the cellular membrane receptor for 10 to 15 minutes.[126] By calculation, insulin is usually administered at the rate of 100 to 200 mU. per minute. Blood samples for glucose determination are drawn from an indwelling catheter in tandem with a heparin lock in the contralateral arm. Since the patient is conscious,* symptoms of hypoglycemia are readily apparent and can be corrected by shutting off the insulin. Total

*Epidural anesthesia is always used.

Table III. Comparison between Dextrostix values and laboratory blood glucose values by AutoAnalyzer during the constant intravenous infusion of crystalline zinc insulin (200 m.U per minute)

	Blood glucose (mg./100 ml.)	
Postoperative hours	*Dextrostix*	*Laboratory*
0-0.5	>250	375
0.5-1	>250	342
1-2	>250	333
2-3	>250	295
3-4	>250	265
4-5	175	183
5-6	130	138
6-7	90	98
7-8	45-90	79
8-9	90	64
9-10	90	86
10-11	45	42
12+	45	58

insulin requirement during the first 24 hours is usually less than 30 U.

Blood glucose is measured every 30 minutes during the first hour post partum and hourly thereafter for up to 12 hours. Since the rapid loss of HPL from the plasma is accompanied by increasing insulin sensitivity,[31] hypoglycemia can be anticipated between 5 and 7 hours post partum. Thus, close observation of the patient by recovery room nursing personnel will avoid any catastrophe associated with a sudden fall in the plasma glucose concentration. When blood is drawn for laboratory analysis, a glucose oxidase–impregnated stick is used to estimate the blood glucose immediately at the bedside. Table III shows the remarkable accuracy of the "stick" method compared to AutoAnalyzer values. Hypoglycemia is simply managed by temporarily discontinuing the insulin infusion and advancing the glucose infusion. The administration of highly concentrated glucose solutions is not necessary.

Hyperglycemia is controlled by increasing the insulin infusion and monitoring the blood glucose concentration more frequently in the opposite arm. In our experience, the blood glucose concentration stabilizes in the first 12 to 18 postpartum hours, a time when oral liquid feeding may be instituted. Within 24 hours of delivery, one may resume the administration of the daily insulin requirement by subcutaneous injection. At this time, however, the daily insulin requirement should be reduced to an amount equal to 60 per cent of the prepregnant dose.

Insulin management in the later puerperium

The release of HGH in response to insulin-induced hypoglycemia is a physiologic attempt to maintain maternal glucose homeostasis through enhanced lipolysis.[39, 127] In the parturient diabetic patient, this phenomenon is absent due to HGH suppression and must be considered when providing for adequate puerperal diet and insulin therapy. During the first four to six postpartum weeks, HGH secretion gradually returns, and with it there is a gradual increase in the daily insulin requirement.

Nursing in the puerperal diabetic patient

Nursing may be beneficial to the postpartum diabetic patient. Unfortunately, scientific data are lacking to support this observation in terms of the metabolic energy/cost relationship between mother and child. Maternal caloric expenditure for mammary milk production is between 600 and 900 calories per day, of which 250 calories may be taken from maternal stores. Milk production occurs de novo from substrates obtained from the maternal vasculature sequestered by the breast and synthesized into specific nutritional components. As far back as 1935, wide fluctuations in the maternal blood glucose concentration were observed in relation to the production of mammary lactose.[128] It is impossible to make specific recommendations at this time yet important to support lactation as a means of maintaining a stable daily insulin requirement.

We have observed an amelioration of diabetes in terms of daily insulin requirement in three parturient diabetic patients. The decline in daily insulin requirement was as much as 50 per cent of the prepregnant insulin requirement. Further decreases in daily insulin requirement were observed where diet was rigidly controlled and physical activity was increased. During a 27 month period of physiologic lactation, one diabetic patient was able to maintain a diet of 3,000 calories and 20 U. of NPH insulin without acetonuria or weight gain. The advantages of nursing in diabetic mothers may be related to more efficient mobilization and utilization of maternal metabolic substrates. Thus, maternal hypoglycemia may be equated not only to prolonged attenuation of growth hormone secretion but also to rapid transfer of maternal glucose to the breast for the purpose of lactose production.

Diagnosis and treatment of ketoacidosis

A most severe complication of uncontrolled diabetes in pregnancy is the development of ketoacidosis.[23] Due to the exaggerated ketone body response to starvation in pregnancy, it is important to differentiate between ketosis due to starvation and that due to uncontrolled diabetes. The presence of excess ketonuria with a blood glucose concentration less than 100 mg. per cent suggests the diagnosis of starvation ketosis

for which the simple management is the administration of intravenous glucose. On the other hand, a blood glucose concentration in excess of 200 mg. per 100 ml., a positive plasma ketone reaction, and an arterial pH below 7.25 associated with a low P_{CO_2} require immediate management for diabetic ketoacidosis. Nausea and vomiting often accompanying either of these conditions, perhaps due to the effect of ketone bodies on gastrointestinal motility. Hypokalemia associated with vomiting should be treated with the appropriate administration of intravenous potassium chloride.

When the glucose concentration is above 200 mg. per 100 ml., it is essential to determine whether ketosis has advanced to ketoacidosis by measuring arterial blood gases and electrolytes. Such procedures should be performed as soon as possible in a hospital environment. The emergency management of diabetic ketoacidosis and hyperosmolar coma is a rapid correction of insulin, fluid, and electrolyte deficits. It should be kept in mind that such deficits will also affect the fetoplacental unit. As ketone metabolism changes with the loss of the normal action of insulin, dehydration occurs through the renal loss of glucose. Also extracellular fluid accumulates which, in turn, promotes the osmotic diuresis. Our management is similar to that reported by Winegrad and Clements[129] and includes the use of hypotonic half normal saline with 2.5 per cent fructose infused at a rate of 15 ml. per minute for the first hour with a gradual reduction thereafter. Insulin is administered *intravenously* in small doses rather than in the classic routine of split doses subcutaneously. The purpose is to provide for a more controlled reduction in the blood glucose concentration without reducing the number of insulin receptors at the cellular level.[126] Continuous bedside monitoring is important in the management of diabetic ketoacidosis; thus, intravenous insulin is used.

During this management, a 30 per cent reduction in the blood glucose concentration will occur in the first four hours of therapy. pH will gradually rise, and subjective improvement will be noted by the patient. The administration of bicarbonate should be limited to those cases where the arterial pH is less than 7.1 with a bicarbonate level of less than 5. Patients in shock or in coma should also receive this therapy. Overcorrection in the pregnant diabetic patient to the point of alkalosis will result in an increased risk to the fetus since the fetoplacental unit will attempt to conserve acid radicals and, therefore, may remain acidotic much longer to its own detriment.

A rule to be followed in the management of a pregnant diabetic patient with ketoacidosis is to identify and treat the underlying cause such as renal disease.

Table IV. Itemization of individual health care expenses related to the management of diabetic pregnancy in The Johns Hopkins Hospital as of June 15, 1975

Test	*Cost*
1. Primary examination	
Routine blood screening	$35.00
Diet consultation	$25.00
Glucose panel	$21.00
Ophthalmologic examination	$25.00
Electrocardiogram	$20.00
2. Follow-up examination with or without hospitalization	
Urinary estriol	@$25.00 each
Glucose determinations	@$3.00 each
OCT	$35.00
Amniocentesis	$20.00
Daily room rate (private room)	$135.00/day
Delivery room charge	$100.00
Daily nursery rate	
Regular	$66.00/day
Intensive nursery care	$250.00/day

Economics of diabetic management in pregnancy

Rigid control of the pregnant diabetic patient is costly yet less so than poor care. Therefore, thought should be given to the cost/effectiveness of one's management. Maintenance of glucose homeostasis is, in our view, a rational way of approaching treatment for it not only reduces the risk of serious side effects such as ketoacidosis but also exposes the patient to more frequent care.

For the last five years, hospitalization time has been reduced but not altogether eliminated as a result of the newer management. Others still view hospitalization as the single most important factor in a successful pregnancy. Evaluation in the hospital for one to two weeks prior to delivery not only serves to detect subtle changes in fetoplacental function but also prepares the mother psychologically for delivery.

Table IV itemizes the health care costs related to diabetes. Prior to the institution of current policies, the average bill for total care of the diabetic patient was $25,700 per pregnancy. With the reduction in the number of hospitalizations necessary for correcting diet and insulin but with a four to six-week stay prior to delivery, the costs were reduced to $10,175, a mean cost of 30 individual admission profiles.

Retrospectively, the best results in pregnant diabetic patients are obtained where special clinical attention is provided by *interested* individuals. Uniform interest may come only through regionalization of diabetic

care, a point made recently by Carrington. Regionalization of health care is a sensitive issue among physicians who often equate it to a reduction in the autonomy of individual practice habits. Nevertheless, regionalization of health care where access to such regional centers is made available to the general practitioner would promote better management of the pregnant diabetic patient.

With overwhelming evidence supporting maternal hyperglycemia as the principal cause of perinatal problems being presented,[18, 21, 130] the reduced cost of care can almost guarantee a live birth. Unfortunately, even today, mistakes can be costly in time, lives, and money.

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What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.

ITEMS

Second International Congress on Twin Studies

The International Society for Twin Studies announces the Second International Congress on Twin Studies, to be held in Washington, D. C., August 29–September 1, 1977. The International Society for Twin Studies was established by the General Assembly of the First International Congress on Twin Studies (Rome, October 28–November 2, 1974) with the purpose of furthering research and social action in all fields related to twin studies, for the mutual benefit of twins and their families and of scientific research. For further information, contact: Dr. Gordon Allen, Chairman, Organizing Committee, Second International Congress on Twin Studies, Clinical Center, 2N252, National Institutes of Health, Bethesda, Maryland 20014.

Fourth National Maternal-Infant Life Conference

The Fourth National Maternal-Infant Life Conference, with the theme, "Attachment—Success and Failure," will be held November 3-6, 1976, at the Radisson South Hotel, 7800 Normandale Blvd., Minneapolis, Minnesota 55435. The fee is $35 for members of the Great Plains Organization for Perinatal Health Care or $75 for nonmembers. The speakers include: Beverly Aure, R.N., Madison General Hospital, Madison, WI; Kathryn Barnard, R.N., Ph.D., University of Washington, Seattle, WA; T. Berry Brazelton, M.D., Harvard University, Cambridge, MA; Mecca Cranley, R.N., Madison General Hospital, Madison, WI; Natalie Dahl, R.N., Madison General Hospital, Madison, WI; Selma Fraiberg, M.S.W., Child Development Project, Ann Arbor, MI; Jane Gray, M.D., Denver's Child Abuse Center, Denver, CO; John Kennell, M.D., Case Western Reserve University, Cleveland, OH; Marshall Klaus, M.D., Case Western Reserve University, Cleveland, OH; Mary Krugman, R.N., Denver, CO; Lewis Leavitt, M.D., Waisman Center, Madison, WI; Howard Osofsky, M.D., Boston, MA; Ross D. Parke, Ph.D., University of Cincinnati, Cincinnati, OH; Gerald Solomons, M.D., University of Iowa Hospitals, Iowa City, IA; Arthur Valenstein, M.D., Cambridge, MA; and Eugenia Waechter, R.N., University of California, San Francisco, CA.

For further information, contact: Ms. Linda McNally, Great Plains Organization for Perinatal Health Care, 202 S. Park St., Madison, Wisconsin 53715. Telephone: (608) 267-6990.

Institutes for Physicians and Nurses in Perinatology

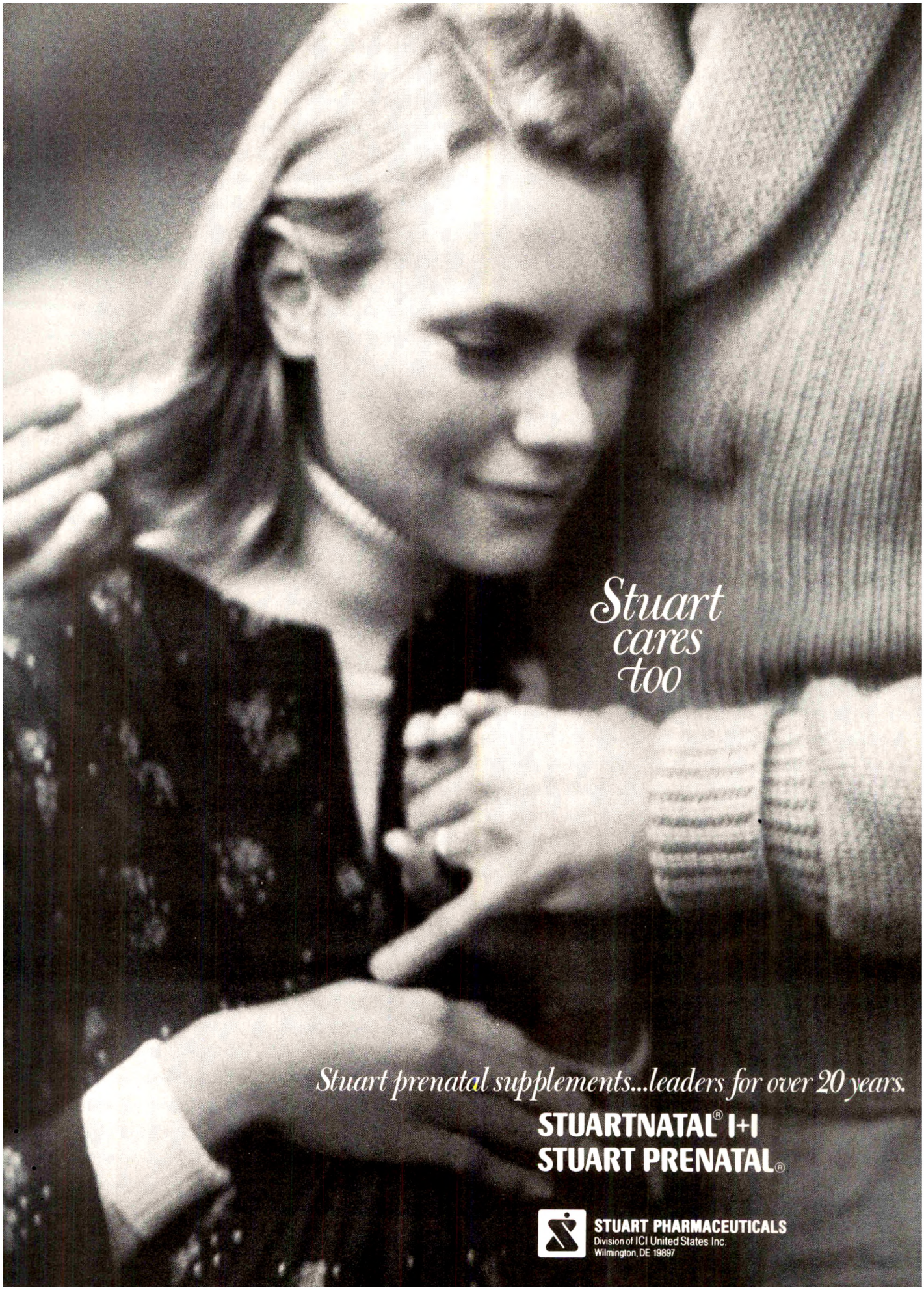
September, 1976, marks the twenty-eighth year of the Institutes for Physicians and Nurses in Perinatology, formerly known as Institutes in the Care of Premature and Other High-Risk Infants, sponsored by the New York State Department of Health and the United States Department of Health, Education, and Welfare and conducted at the New York Hospital–Cornell Medical Center four times during the academic year, with a stipend provided to help cover expenses during attendance. Further information is obtainable by writing: Box 143, Institutes in Perinatology, Department of Pediatrics, New York Hospital, 525 E. 68th St., New York, New York 10021.

International Symposium on mucus in health and disease

An International Symposium on mucus of the gastrointestinal, respiratory, and urogenital tracts, in health and disease, will be held at the University of Surrey, England, on September 13-16, 1976.

The Symposium, which is intended to provide a forum for the interchange of ideas between clinicians and scientists of different specialties and disciplines, will comprise plenary sessions on the structure, function, and regulation of mucus, mucus in disease, and treatment of abnormal conditions. Open sessions for free communications, and workshops to promote the cross-fertilization of ideas are planned.

Accommodation will be provided on the University campus at Guildford, an old market town near London's airports. A Ladies Programme is also arranged. Further details and registration forms may be obtained from: "The Secretariat, Mucus Symposium," Department of Biochemistry, University of Surrey, Guildford, Surrey, GU2 5XH, England.


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Flagyl®

(metronidazole) 250 mg.

Warning

Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

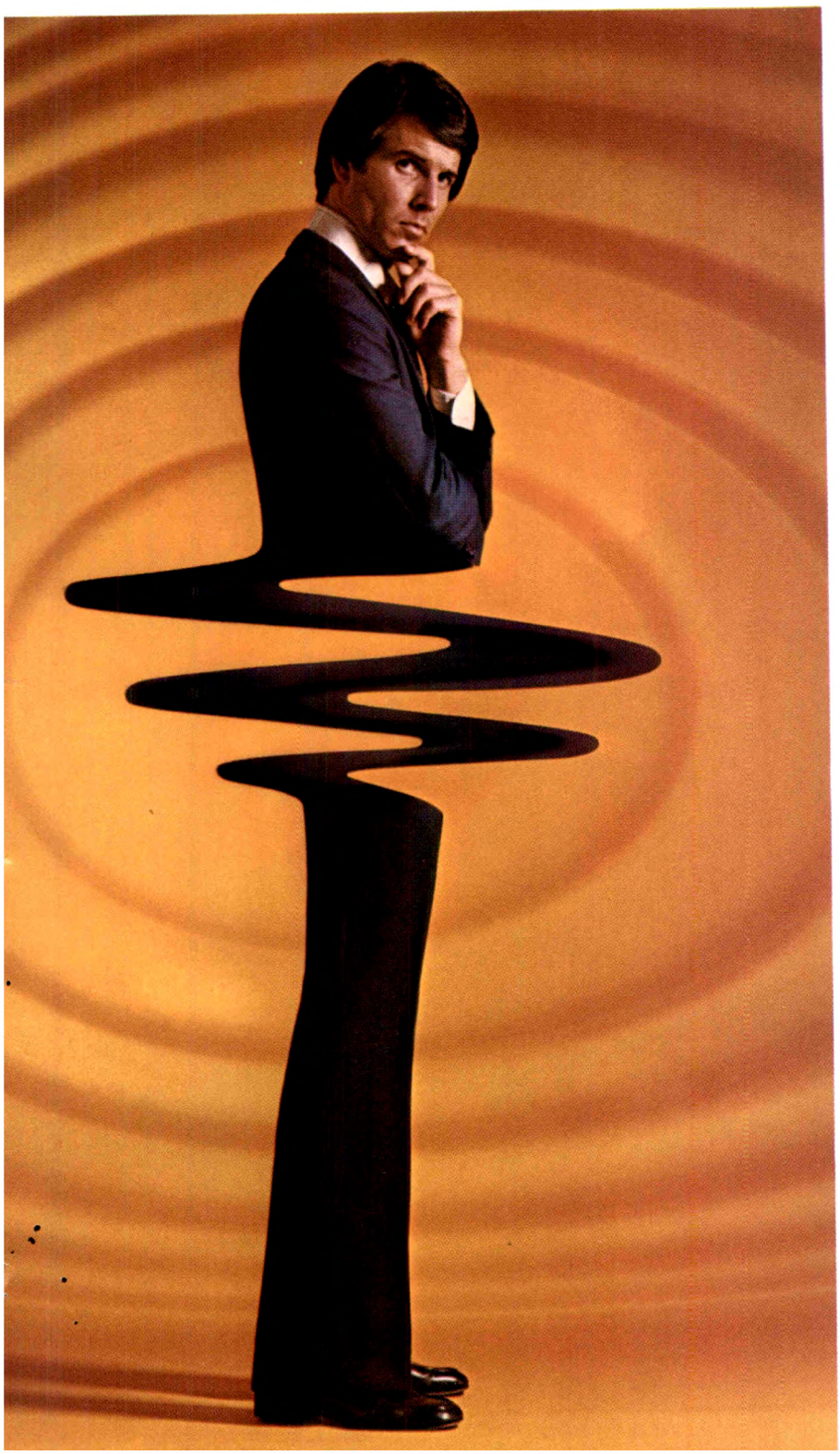
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

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(metronidazole)



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In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra and the bladder. Only the systemic action of Flagyl can eliminate trichomonads from these sequestered sites.

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Flagyl®
(metronidazole)
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Happy homecoming for the new mother

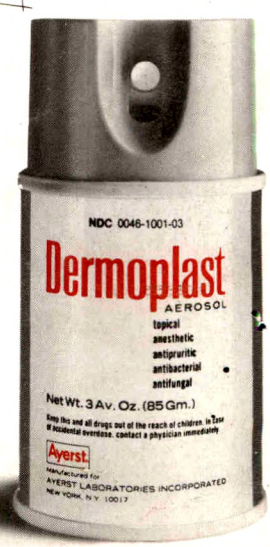


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DERMOPLAST Aerosol Spray contains: Benzocaine, w/w 4.5%; benzethonium chloride, w/w 0.1%; menthol, w/w 0.5%; oxyquinoline benzoate, w/w 1.2%; and methylparaben, w/w 2.0%. Inactive ingredients, vegetable oils and propellant. Also contains 1.9% isopropyl alcohol.

For additional indications, full directions for use, and warnings, see label copy on DERMOPLAST Aerosol Spray can.



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August 15, 1976
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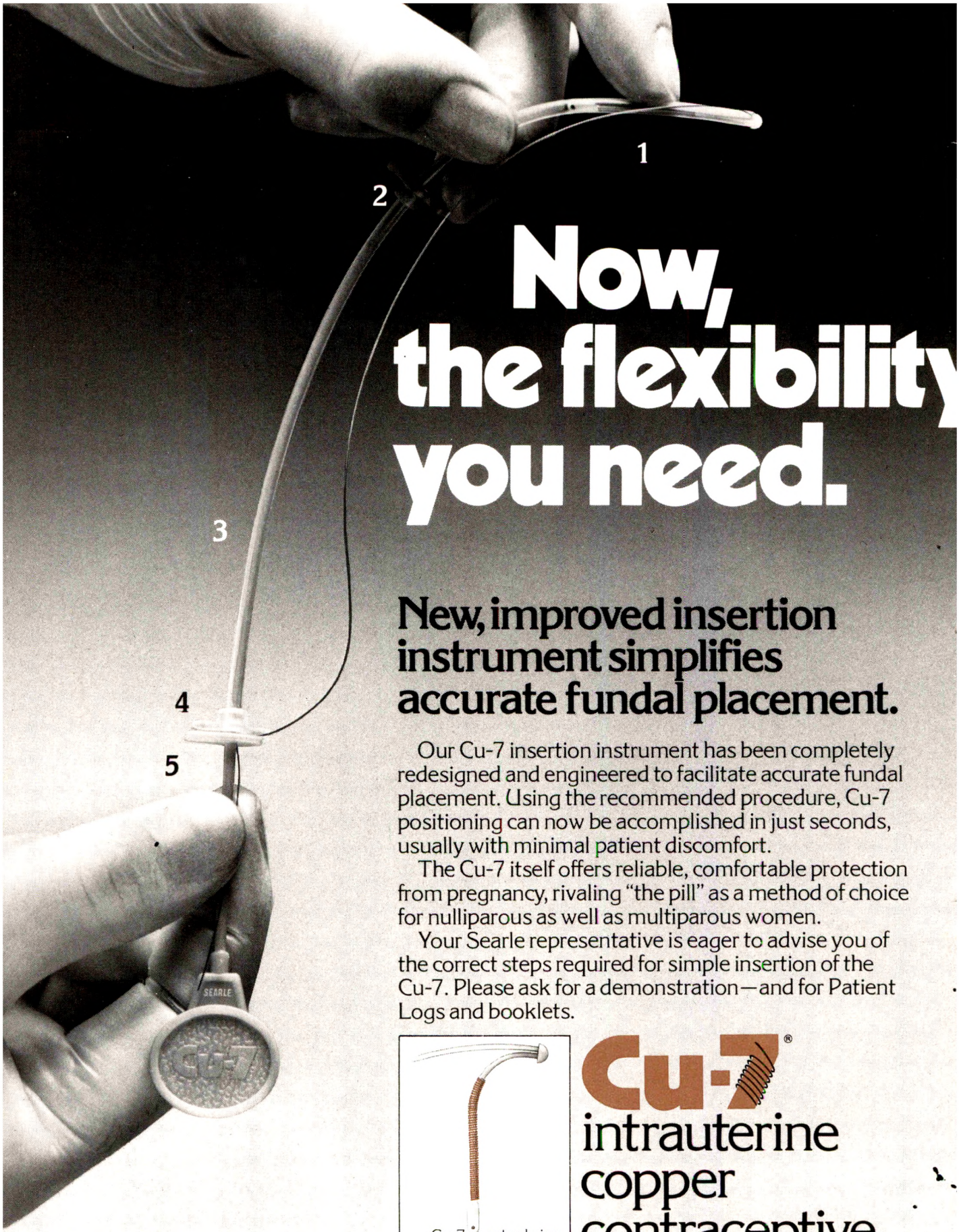
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New, improved insertion instrument simplifies accurate fundal placement.

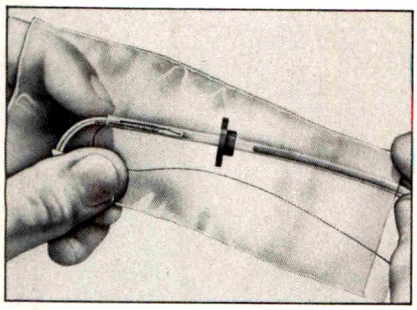
Our Cu-7 insertion instrument has been completely redesigned and engineered to facilitate accurate fundal placement. Using the recommended procedure, Cu-7 positioning can now be accomplished in just seconds, usually with minimal patient discomfort.

The Cu-7 itself offers reliable, comfortable protection from pregnancy, rivaling "the pill" as a method of choice for nulliparous as well as multiparous women.

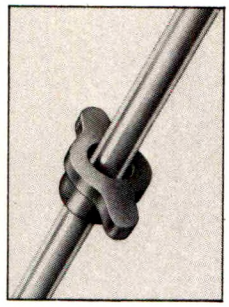
Your Searle representative is eager to advise you of the correct steps required for simple insertion of the Cu-7. Please ask for a demonstration—and for Patient Logs and booklets.

Cu-7®
intrauterine copper contraceptive

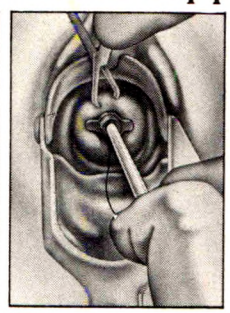
How five newly designed features make it easier to use Cu-7® intrauterine copper contraceptive.



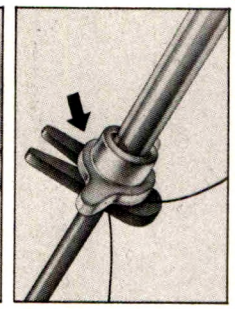
1. New sterile sheath
Helps maintain sterility during loading procedure and cervical-stop setting.



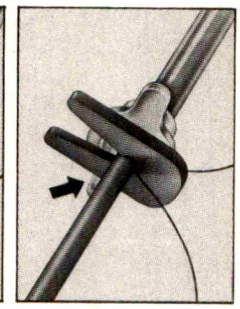
2. New blue-winged cervical stop
A visual guide to aid in correct positioning of the "seven" in the uterus.



3. New flexible rod
Facilitates insertion of "seven" into virtually any normal uterine cavity in seconds.



4. New welded tube-stop
Serves as handle for withdrawing the tube and removal of instrument.



5. New thread-retaining clip
When held to tube-stop during procedure, facilitates insertion and makes tube-crimping virtually impossible.

Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is 89 mg. of pure, virgin electrolytic copper wire providing 200mm^2 of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the copper coil into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication: The Cu-7 is indicated for contraception.

Contraindications: The presence of any of the following, at the time of insertion, constitutes a contraindication: pregnancy, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infected abortion in the past three months, endometrial disease such as hyperplasia or carcinoma and a known or suspected allergy to copper.

Warnings: Recent reports suggest an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. In some cases, initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned of the suggested incidence of increased risk of sepsis and followed with close vigilance.

The long-term effects on the offspring of the presence of copper in the uterus during pregnancy are unknown.

Perforations of the uterus have occurred. In this case the device should be removed immediately.

The use of microwave therapy in patients with metal prosthetics may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients wearing a Cu-7.

Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease, the incidence of which is one in two hundred thousand.

Precautions: A pelvic examination should be done.

Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed shortly following a menstrual period. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed.

Occasional perforations of the uterus (.03%) have been reported, usually during insertion into patients less than two months post abortion or post partum. If penetration into abdominal cavity occurs, laparotomy should be performed and the device recovered. Local inflammatory reaction with abscess formation is a possibility if a device is left in the abdomen.

If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

The Cu-7 should be removed if pelvic infection which is unresponsive to treatment occurs.

The device should be replaced every two years. There is no evidence of decreasing effectiveness with time before two years, but the contraceptive effectiveness of the Cu-7 after two years has yet to be established.

If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to pull on the thread and displace the Cu-7 and told to return in two years for its replacement.

A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman wearing a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being worn.

Adverse Reactions: Perforation of the uterus has occurred.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women.

Insertion cramping, usually of no more than a few seconds' duration, may occur; however, some women may experience residual cramping for several hours or even days. Transient spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. The following complaints have also been reported, although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, and cystitis.

Dosage and Administration: A single Cu-7 is to be inserted into the uterine cavity (see Precautions section). The small diameter of the Cu-7 enables easy insertion into the nulliparous as well as the multiparous uterus. Present information indicates that the efficacy is retained for at least 24 months. Until accurate data indicating a longer effective life become available, the Cu-7 should be removed and a new one inserted on or before 24 months from the date of insertion. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

How Supplied: Available in cartons of 6 and boxes of 30 sterile units (Cu-7 with an inserter) and sufficient patient identification cards.

Clinical Studies: Different event rates have been recorded with the use of different intrauterine contraceptive devices, inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use.) This experience encompasses 321,699 woman-months of use, including 12 months for 9,594 women and 24 months for 7,599.

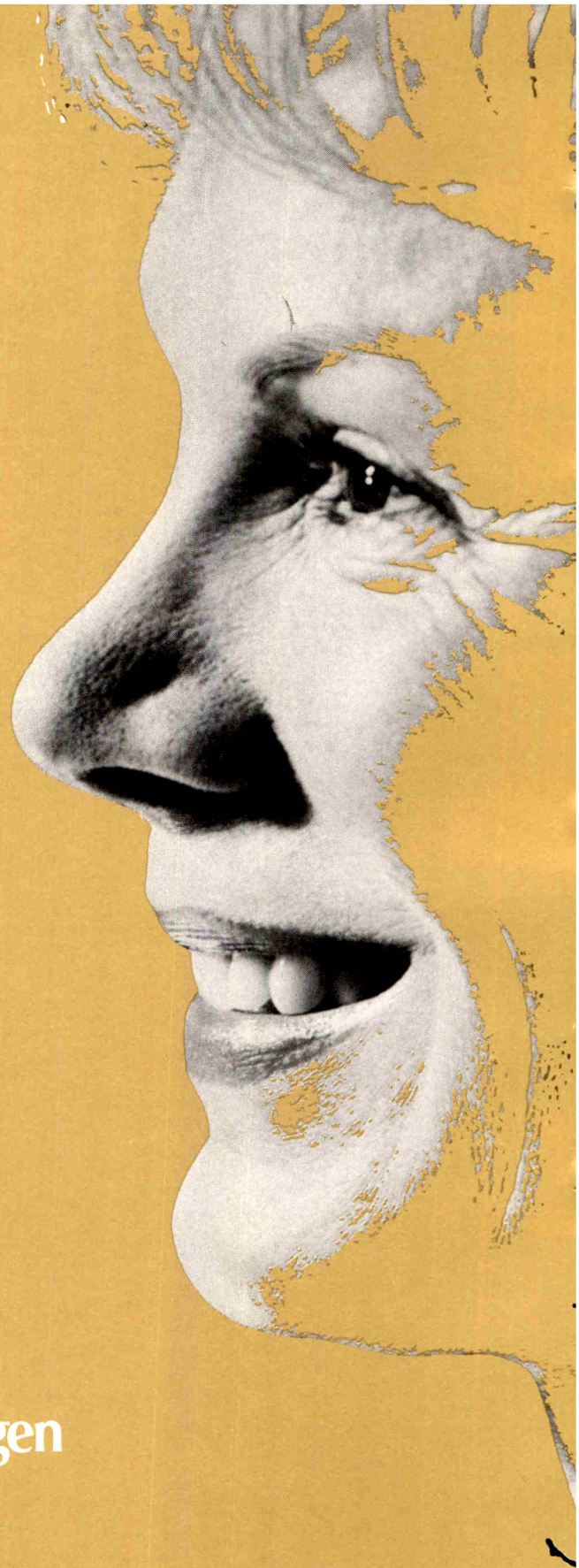
	12 Months		24 Months	
	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.7	1.3	2.5	2.1
Expulsion	5.5	7.7	6.5	8.7
Medical Removal	9.6	12.7	15.3	18.2
Continuation Rate	78.3	72.9	68.9	59.7

Please see complete product labeling for insertion and removal techniques.

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Estrogen replacement therapy moves forward



the major human estrogen micronized for oral effectiveness

Estrace®
(estradiol)

1-mg. and 2-mg. scored tablets

- not esterified, not conjugated
- estradiol...the active estrogen at the cellular level

from Mead Johnson

overall, 95% of patients studied gained adequate or complete relief of their symptoms[1]

Estrace (estradiol) was given to 369 estrogen-deficient women for periods ranging up to a year or more (average of six months); 319 of these women received an initial dosage of 1 or 2 mg. per day and were evaluated for efficacy. *Complete disappearance* of hot flushes was experienced by 227 (76%) of 298 women, of sweating by 131 (80%) of 164 women, of tingling by 62 (94%) of 66 women, and of genital atrophy by 44 (88%) of 50 women. In general, 95% of the patients evaluated experienced either adequate or complete relief of their symptoms. Remarkably, in 77% of the patients, symptoms were controlled without need to adjust the initial dosage—usually 2 mg. daily. (Dosage after adjustment ranged from 1 mg. to 3 or 4 mg. a day.)[1]

cyclic therapy recommended

Recently, published reports of retrospective human data have emphasized that patients using estrogens may have an associated increased risk of endometrial cancer. This information makes cyclic rather than continuous estrogen replacement therapy even more prudent. (See brief summary.)

With Estrace, treatment should be initiated with a dose of 1 or 2 mg. daily and then adjusted to the lowest dose possible still maintaining the relief of symptoms. The usual regimen for cyclic administration of Estrace is three weeks on drug, followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4–6 days) to prevent recurrence of menopausal symptoms.

estradiol... orally effective

The technique of micronization has opened up the oral route to natural human estrogen replacement with Estrace. Reduced particle size of the estradiol in Estrace makes effective gastrointestinal absorption possible. Onset of action is rapid, with marked increases in levels of circulating estradiol and estrone; concomitant decreases in serum concentrations of FSH and LH are sustained over a 24-hour period.[2]

Because estradiol can be assayed in plasma, Estrace can provide objective[2] as well as clinical evidence[1] of ready availability and biologic activity.

well accepted by patients[1]

In the 369 patients previously described, the incidence of estrogen-induced side effects with Estrace was relatively low. Incidence of nausea was remarkably low—only 2% of patients before dosage adjustment. Some patients who had complained of this problem while on conjugated equine estrogens reported its complete disappearance on changing to Estrace. Whereas before dosage adjustment 24% experienced breast tenderness, 31% edema, 18% (of 151 with intact uteri) bleeding, and 4% weight gain, only about 2% of the 369 patients dropped out because of side effects.[1]

long-term therapy should be monitored

A few instances of significant gynecologic disease became apparent during clinical investigations.[1] Endometrial hyperplasia was discovered in seven patients, all of whom had previously received estrogen therapy for one to three years prior to entering the study. One patient was reported to have carcinoma *in situ* and another showed adenocarcinoma of the endometrium. In clinical practice, the physician should be alerted to the potential of thrombotic disorders and be prepared to discontinue medication immediately if they occur. Because of variations in normal endogenous hormone production, certain patients may exhibit signs of excessive estrogenic stimulation. Adverse reactions generally associated with estrogen administration may occur and these are listed in the brief summary. Prior to initiation of treatment with Estrace or any other estrogenic preparation, an adequate physical examination should be given.

References

1. Callantine, M.R., *et al.*: Micronized 17β-estradiol for oral estrogen therapy in menopausal women, Obstet. Gynecol. *46*:37–41 (July) 1975.
2. Yen, S.S.C., *et al.*: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β-estradiol in postmenopausal women, J. Clin. Endocrinol. Metab. *40*:518–521 (March) 1975.

For Brief Summary, please see following page.

Estrogen replacement therapy moves forward...

Estrace® (estradiol)

the major human estrogen micronized for oral effectiveness



Indications: Estrace® (17β-Estradiol) is indicated for relief of endogenous estrogen deficiency and associated menopausal symptoms.

Contraindications: Estrace® is contraindicated in patients with 1) markedly impaired liver function; 2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal, or in men in whom castration is not feasible; 3) known or suspected estrogen dependent neoplasia, such as carcinoma of the endometrium; 4) undiagnosed abnormal genital bleeding; 5) thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions; and 6) pregnancy.

Warnings: The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If these occur or are suspected the drugs should be discontinued immediately. Discontinue medication pending examination if there is a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time. Hypercalcemia may occur in as many as 15% of breast cancer patients with metastases and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of untoward effects such as progression of the cancer or hypercalcemia, estrogen medication should be stopped. A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, edema, etc. Because of estrogen induced salt and water retention, these drugs should be used with caution in patients with epilepsy, migraine, asthma, cardiac or renal disease. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. In the event that any unexplained or excessive vaginal bleeding would occur while on estrogen therapy, nonfunctional causes should be borne in mind. The drug should be discontinued and a thorough investigation made as to the cause, being certain to rule out the possibility of malignancy. Pre-existing uterine fibromyomata may increase in size while using this product, therefore, patients should be examined at regular intervals while receiving estrogenic therapy. Women with a strong family history of cancer, recurrent chronic cystic mastitis, or abnormal mammograms should be administered estrogens with caution. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete. A pre-treatment physical examination should include special reference to breast and pelvic organs as well as a Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of animals. When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females. Prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired. Continuous use of estrogens will result in prolonged stimulation of the endometrium and breast. In order to avoid this, oral estrogens should be administered cyclically in the menopausal or hypogonadal patient. The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric. Certain endocrine and liver function tests may be affected by treatment with estrogens. If such tests are abnormal in a patient taking these drugs it is recommended that they be repeated after the drug has been withdrawn for two months. Any possible influence of prolonged estrogen therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study.

Adverse Reactions: A statistically significant association has been demonstrated between use of estrogen-progestin oral contraceptives and the following serious reactions: Thrombophlebitis, pulmonary embolism, and cerebral thrombosis. Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious reactions: coronary thrombosis and neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis). The following adverse reactions are known to occur in patients receiving estrogens: nausea, vomiting, anorexia, gastrointestinal symptoms (such as abdominal cramps or bloating), edema, breakthrough bleeding, spotting or withdrawal bleeding, breast tenderness and enlargement, change in body weight (increase or decrease), headache, increased cervical mucus, allergic rash, loss of libido and gynecomastia in the male, reactivation of endometriosis, aggravation of migraine headaches, hepatic cutaneous porphyria becoming manifest, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, cystitis-like syndrome, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, possible diminution in lactation when given immediately post-partum, irritability, and malaise.

Important Notes: An increased risk of thromboembolic disease associated with the use of oral contraceptives containing estrogens and progestins has now been conclusively established. Retrospective studies have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of these drugs. There have been three principal studies in Great Britain[1-3] and one in the United States[4] leading to this conclusion. As a result of these studies, it has been estimated that users of oral contraceptives containing estrogens are 4 to 7 times more likely than non-users to develop thromboembolic disease without evident cause. The American study also indicated that the increased risk did not persist after discontinuation, nor was it enhanced by long continued administration. Although the American study was not designed to evaluate a difference between products, it did suggest that there might be an increased risk of thromboembolic disease in users of sequential products. Confirmation of this finding requires further study. In a more recent analysis of data derived from several national adverse reaction reporting systems,[5] British investigators concluded that the risk of thromboembolism, including coronary thrombosis, is directly related to the dose of estrogen used in oral contraceptive products. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. Nevertheless, in view of this study, as well as others that have demonstrated a positive relationship between estrogens and thromboembolism, it would seem prudent and in keeping with basic therapeutic principles, to utilize, whenever feasible, the smallest effective dose of estrogen in treating patients. Risks associated with certain other known adverse reactions, such as elevated blood pressure, liver dysfunction, and reduced tolerance to carbohydrate, have not as yet been quantitated. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be confirmed nor refuted at this time. Close clinical surveillance of all women taking estrogens must be continued. It has been reported in a recent study done in the United States[6] that the maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

(1) Royal College of General Practitioners: Oral Contraception and Thrombo-Embolic Disease. J. Coll. Gen. Pract. 13:267-279, 1967. (2) Inman, W.H.W. and Vessey, M.P., Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women in Childbearing Age, Brit. Med. J., 2:193-199, 1968. (3) Vessey, M.P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969. (4) Sartwell, P.E., Masi, A.T., Arthes, F.G., Greene, G.R., and Smith, H.E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969. (5) Inman, W.H.W., Vessey, M.P., Westerholm, B., Engelund, A., Thromboembolic Disease and the Steroidal Content of Oral Contraceptives. Brit. Med. J., 25th April, 1970. (6) Herbst, et al. — Adenocarcinoma of the Vagina — New England Journal of Medicine, Vol. 284, Number 16 (April 22, 1971).

Dosage and Administration: Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol. Dosage may be adjusted to control the presenting symptoms depending on the response of the individual patient; the minimal effective dose for maintenance therapy should be determined by titration. To avoid continuous stimulation of the reproductive tract and breasts, cyclic therapy is recommended. The usual regimen consists of three weeks on drug followed by one week off drug. Some patients may require a slightly shorter estrogen-free interval (4-6 days) to prevent recurrence of menopausal symptoms. Withdrawal bleeding of unusual amount or duration should be investigated.

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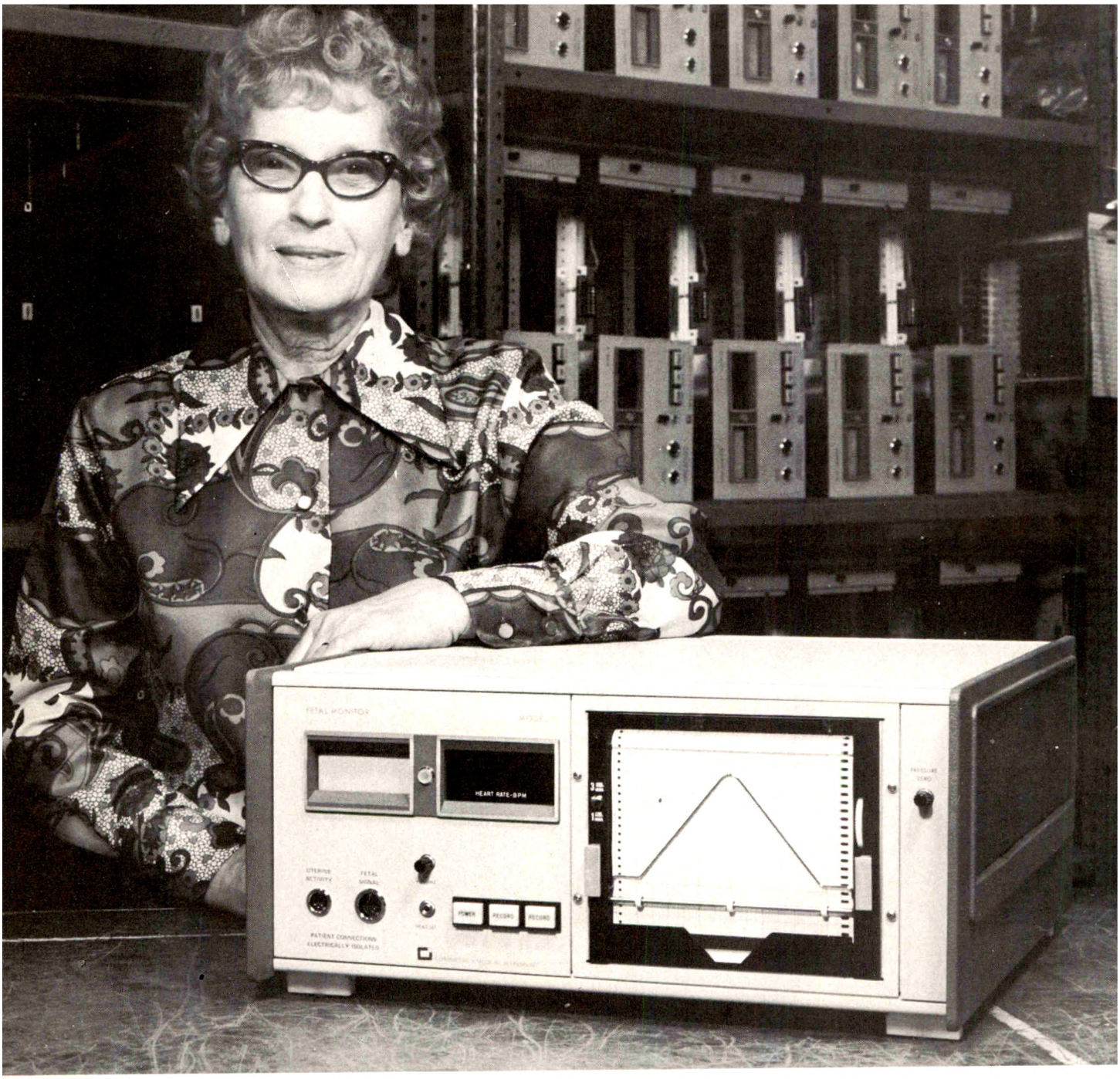
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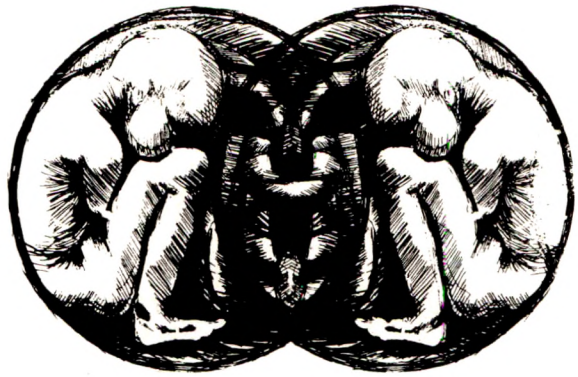
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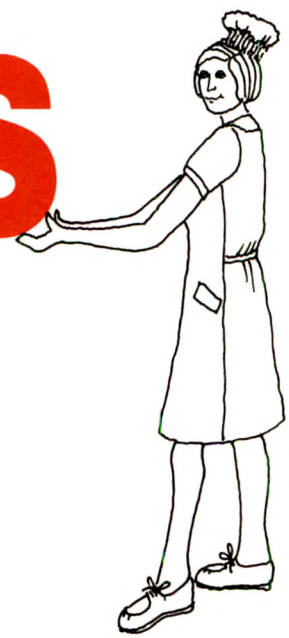
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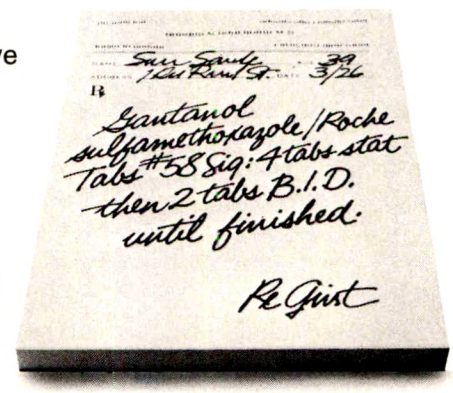
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Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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1. Davis, J.E. et al.: Comparative evaluation of MONISTAT and Mycostatin in the treatment of vulvovaginal candidiasis, *Obstet Gynecol* 44:403 (Sept) 1974.

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Incidence of Breakthrough Bleeding in Clinical Trials					Total Cycles
Cycle	1	12	24	36	20,312
Breakthrough Bleeding	9.0%	3.1%	2.1%	2.3%	3.0%

The incidence of breakthrough bleeding remained very low in patients switched from other oral contraceptives as well as in patients "fresh" to hormonal treatment. *These latter patients were considered "fresh" if more than 90 days had elapsed since previous hormonal treatment or if they were more than 70 days postpregnant.

Incidence of breakthrough bleeding among women "fresh" to oral contraceptives or switched from other oral contraceptives

	"Fresh" to Oral Contraceptives	Switched from Other Oral Contraceptives	Statistical Difference
Breakthrough Bleeding	2.7%	3.1%	Not Significant

Unsurpassed effectiveness despite low dose

LO/OVRAL contains only 0.3 mg. norgestrel and 0.03 mg. ethinyl estradiol. Yet contraceptive effectiveness is unsurpassed. In clinical trials among 1633 women for a total of 20,312 cycles, only two pregnancies were reported. This, according to Pearl's formula, represents a pregnancy rate of 0.13 per 100 woman-years' usage.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions should avoid any oral contraceptives. The SPECIAL NOTE, Contraindications, Warnings, Precautions and Adverse Reactions in the accompanying IN BRIEF should be carefully considered.

See important information on next page.

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IN BRIEF:

SPECIAL NOTE: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thrombotic, thromboembolic, and cerebral-vascular disease, associated with the use of hormonal contraceptives, has been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported, and appropriate tests should be conducted to monitor these during oral-contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS: LO/OVRAL® is indicated for oral contraception.

CONTRAINDICATIONS: 1. Thrombophlebitis, thromboembolic disorders, cerebral-vascular disease, coronary-artery disease or a past history of any of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

WARNINGS: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism, and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral-vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three[4-7] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a non-user group. This study in its interim analysis states: "A statistically significant higher rate of reporting of cerebrovascular accidents in takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to non-users.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College study indicated that the degree of risk was not associated with duration of treament.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in non-users. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral-contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery. 2. An increased risk of myocardial infarction associated with the use of oral contraceptives has recently been reported supporting a previously suspected association.[13,14] Two separate retrospective case-control studies relating to fatal and non-fatal myocardial infarction in users and non-users of oral contraceptives in Great Britain were reported in May of 1975.[13,14] These studies estimate that the increased risk of hospital admission for myocardial infarction among users of oral contraceptives as compared to non-users was 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; the risk of death associated with the use of oral contraceptives as compared to non-users was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that, although use of oral contraceptives was a risk factor per se, users who had myocardial infarction were more likely to also have additional underlying risk factors for coronary artery disease, such as heavy smoking, hypertension, diabetes, pre-eclamptic toxemia, obesity, and type II hyperlipoproteinemia. 3. Discontinue oral-contraceptive medication if there is: gradual or sudden, partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal-vascular lesions. 4. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[11,12] The safety of LO/OVRAL® in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. 5. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time. 6. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. Such lesions have been reported in short-term as well as long-term users of oral contraceptives.

PRECAUTIONS: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smears, since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver-function tests may be affected by treatment with LO/OVRAL. Therefore, if such tests are abnormal in a patient taking LO/OVRAL, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged LO/OVRAL® therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving LO/OVRAL therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with LO/OVRAL may mask the onset of the climacteric. 10. The pathologist should be advised of LO/OVRAL therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, LO/OVRAL® should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during LO/OVRAL therapy.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, myocardial infarction, cerebral thrombosis and hemorrhage, gall bladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis, hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, breast changes: tenderness, enlargement and secretion, change in weight (increase or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX, and X, decrease in antithrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine, and decrease in T^3 uptake values; metyrapone test; and pregnanediol determination.

NOTE: For more specific details on LO/OVRAL and LO-OVRAL-28, refer to package inserts.

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CLINICAL OPINION

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Potencies of oral contraceptives

RICHARD A. EDGREN, PH.D.

F. M. STURTEVANT, PH.D.

Ann Arbor, Michigan, and Chicago, Illinois

Oral contraceptives are combinations of estrogens and progestogens or, in the case of the mini-pills, progestogens alone. With specific test procedures in laboratory animals or human subjects, it is possible to assign potency evaluations to the components relative to the progestational, estrogenic, or antiestrogenic activities of the progestogen or to the estrogenic potencies of the estrogenic component. It might even be possible to quantify the synergistic effects of the estrogen on the progestational agent. Unfortunately, however, it is impossible now to amalgamate such assay results into single estimates of the potencies of the combinations (either the combination products per se *or the combination tablets of sequential products). For example, an over-all estrogenic potency of a combination preparation would involve the integration of contributions from the estrogen itself plus the estrogenic products of metabolism of the progestogen minus the antagonistic effect of the progestational agent, if any. These factors cannot now be quantified independently, much less merged into a single figure of clinical significance. Further, even if it were possible to produce such an estimate, it is unlikely that the evaluation would be meaningful in relation to any putative side effect or adverse reaction, i.e., the alleged thrombogenic effects of oral contraceptives cannot currently be related directly to any measure of potency that will allow prediction of these clinical conditions from laboratory models. Any evaluation of the potential of a given contraceptive to produce a specific side effect will depend upon data generated with specific regard to that adverse reaction and the individual product in question.*

From Parke, Davis & Company and Searle Laboratories.

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ALTHOUGH oral contraceptives have been subjected to clinical evaluation for two decades, have been marketed for 15 years, and have been uniquely scrutinized for possible adverse effects for more than a

decade, little in the way of significant danger to the contraceptor has been demonstrated for these materials. Our opinion, expressed here, appears to be supported by the recent report of the Royal College of General Practitioners.[1] However, continued suspicions are reflected by some authors and these problems are frequently related to the "potency" of specific contraceptive preparations or their components. We shall not concern ourselves here with the reality, or lack thereof, of causal association of any given untoward reaction and the oral contraceptives; we and others have discussed this problem elsewhere and, we believe, proof remains unavailable for serious conditions. We shall, however, consider the problem of oral contraceptive potency. We feel that any simple listing of commercial preparations in order of potency, whether it be progestational, estrogenic, or some combination, would be simplistic and that any effort to relate side effects in terms of such a listing is likely to be misleading.

Some basic definitions

Oral contraceptives include three types of preparations: (1) the conventional contraceptives that require the administration of an estrogen and a progestational agent simultaneously for a portion of the menstrual cycle (2) the sequential contraceptives that require administration of estrogen alone for the first portion of the cycle followed by a period of administration of estrogen-progestogen combination for the last few days before withdrawal of medication, and (3) a series of progestogen-alone contraceptives, or "mini-pills," which involve continuous progestogen administration, unrelated to the cycle.

In (1) and (2) above, contraception presumably results from blockade of ovulation, which can be largely accounted for by the estrogenic components. This blockade of ovulation is apparently a tertiary effect: The primary effect appears to be at the level of the hypothalamus, where the estrogen inhibits the releasing hormone LRF. This material functions in releasing luteinizing hormone (LH) from the pituitary. LH stimulates ovulation. Thus, the actual antiovulatory effect of the estrogen is three stages away from the point of action of the estrogen itself. Most investigators believe that this is the primary contraceptive action of the estrogen-containing oral contraceptives. In the case of the sequential agents, where only estrogen is administered at the probable time of ovulation, the contraceptive effect must depend entirely upon estrogenic effects, presumably ovulation blockade. Of course, other activities could occur and must be considered. For example, during the first few days post coitum, estrogens will accelerate or inhibit (dose dependent) the transport of the egg through the oviduct. Animal studies suggest that low doses accelerate transport of the eggs, which arrive in the uterus too early for nidation. The blockage of transport (tubal lock) occurs only at high dose levels in some species. The postcoital use of diethylstilbestrol, which has been discussed extensively in the United States over the past few months, may reflect these effects. However, since massive doses of diethylstilbestrol or ethinyl estradiol are required in women, it is difficult to believe that the 50 to 100 μg of estrogen administered in most oral contraceptives could have this effect. An antinidatory effect, resulting from activity at the level of the endometrium, is also possible but poorly documented. In summary, we believe that the antiovulatory effect of the estrogenic agents is the primary contraceptive activity of combination and sequential contraceptives.

The role of the progestogen in the oral contraceptive then becomes moot. Again a role is suggested by the effects of the few days of progestogen in the sequential products. Cyclic mestranol or ethinyl estradiol will result in irregular menstrual patterns during withdrawal. These are usually copious and extended in period: they are uncontrolled. The administration for 4 or 5 days of a progestational agent, prior to withdrawal, results in a more satisfactory "bleed-off" in these patients. The main role of the progestational agents in contraceptives is the control of the endometrial bleeding pattern, i.e., the precise control of the cycle.

It seems likely, however, that the progestational agents also contribute something to contraception per se. Many studies have indicated that approximately 95 per cent of the cycles of patients who receive oral contraceptives show pregnanediol excretion levels commensurate with ovulation inhibition. Thus escape ovulation is suggested in approximately 5 per cent of cycles. However, observed failure rates for oral contraceptives in controlled studies are not commensurate with the hypothesis of a 5 per cent escape ovulation. The pregnancy rates with the sequentials establish the rate of pregnancy to be expected exclusively from estrogen effects, i.e., a rate of no more than one to two per 100 woman-years.

Mini-pills are associated with even higher pregnancy rates than the sequentials. Their mode(s)-of-action are unclear; it was originally believed that they had little antiovulatory action. It now appears that pituitary block is evident in 50 per cent or more of "cycles" on progestogen-only contraceptives.[2, 3] However, the main contraceptive effect appears to be at the level of

cervical mucus, which fails to show normal midcycle liquifaction under treatment. The drawback to this type of therapy is the high rate of menstrual abnormality. In large-scale, long-term studies, some 60 to 80 per cent of patients and 30 to 50 per cent of cycles show abnormal bleeding patterns. Practical experience led to the composition of oral contraceptives containing combinations of estrogens and progestogens and it would seem that neither component independently provides a fully satisfactory contraceptive.

The use of oral contraceptives over the past 20 years has been accompanied by a number of difficulties, some real and some imagined. Our puritanical background may be reflected in some of the objections to the use of oral contraceptives and in the horrified finger-pointing associated with minor side effects. However, certain major problems may be associated with the oral contraceptives, at least in a statistical sense. The most crucial, at least now, appears to be thromboembolic phenomena. The history of this problem need not be discussed here. Earlier statistical data on thromboembolic phenomena were from retrospective, case-control ("trohoc"[3a]) studies, and led to two suggestions or extrapolations: (1) that contraceptors had a higher rate of thrombotic episodes than women who were not on oral contraceptives, and (2) the higher the dose of estrogen the higher the frequency of episodes. The deficiencies in trohoc methods need no further discussion here, particularly with respect to the presumed correlation of dosage with incidence of episodes. In an effort to resolve these problems, it appeared desirable to some commentators to have a listing of oral contraceptives in order of "estrogenic potency." In this statement, we shall survey the data on the oral contraceptive preparations, which will demonstrate that no linear series of potency or activity relationships can be defined, and that no relationships can be drawn between rates of thrombotic episodes or for any coincidental adverse occurrence and the relative potencies of the drugs as usually defined.

Three separate considerations are germane to this type of listing: (1) it would seem critical to understand the relative potencies of the various progestational agents, (2) it would be important to know the estrogenicity of these agents, and (3) the estrogen antagonistic actions of most of the progestogens must be understood. Most of the oral contraceptives are combinations of an estrogen with a progestogen that has certain estrogenic effects; dealing with the potential additivity of the component estrogen plus the estrogenicity of the progestogen becomes critical. Further, most of the progestogens are also antiestrogens, at least on certain targets; the influence of this antagonism on the over-all estrogenic activities of a combination needs consideration. These interactions are not simple problems due to variations among different target organs (for example, at a single dose combination testosterone will inhibit the action of estrone on the rat vagina but add to the estrogenic effect on the uterus). Also, the progestogens are not competitive inhibitors of the estrogens at the estrogen receptor in the uterus. We are unable at this time to define the precise nature of the antagonism in the uterus where it has been intensively studied. The consideration of any possible progestational modification of any putative thrombogenic effect of the estrogen simply compounds hypothesis with speculation.

Before continuing with this problem, let us ask the question, what is meant by "potency"? From a very strict, purely pharmacologic pointed of view, potency may be defined as being simple quantitative biological differences between substances that are otherwise qualitatively identical.

Technically, the potency of any given drug must be related to another drug (called the "standard") and is evaluated by measuring the separation of the parallel dose-response curves. The relative potency so calculated is valid only so long as the following variables, among other variables, are identical: (1) the species and often strain of animal (race in man?), (2) the target organ or tissue involved, (3) the specific pharmacodynamic response of the organ or tissue, (4) the temporal variables, i.e., time of assessment following dosing at a specific time of day (and season, etc., if relevant), and (5) the route of, and vehicle for, drug administration. The slopes of the dose-response curves must not differ significantly and randomization must be assured. Assays may be quantitative or quantal, parametric or nonparametric.

Progestational potency

The classic methods of comparing progestational potency, the Clauberg test in rabbits or the Swyer-Greenblatt delay-of-menses test in human beings, focus on these restrictions as critical problems. In the Clauberg test, all qualitative evaluations of histologic development of the endometrial glands, and the slopes of the dose-response curves, must be identical among progestogens for potency to be meaningful. When slopes are nonparallel, potency estimates become meaningless; however, arbitrary decisions are often made. The differences in slopes of dose-response curves for protestogens in the Clauberg test have been evident for years. In the Swyer-Greenblatt test, we are

Table I. Postponent of menstruation assays: Various progestogens*

Drug	*No. of observations*	*Approx. ED_{50} (mg.)*
Norethisterone	89	4.25
Norethisterone acetate	51	10.5
Norethynodrel	16	20
Norethynodrel + mestranol (Enovid)	28	5.3
Provera	4	>10
Provera + mestranol	21	22.5
Megestrol acetate	30	>10
Megestrol acetate + mestranol	51	1.8
Melengestrol acetate	17	>10
Melengestrol acetate + mestranol	16	2.5
17α-vinyl-19-nortestosterone (SC4641)	12	>10
17α-vinyl-19-nortestosterone + mestranol	13	7
21-fluoro,Δ6,6-methyl-17α-acetoxyprogesterone (SC10230) + mestranol	4	<2.5
Ethynodiol diacetate	9	>4
Ethynodol diacetate + mestranol	32	1.5
Gestovis	7	>20
Gestovis + mestranol	22	>10
Enol luteovis	1	>50
Enol luteovis + mestranol	4	>25
Didrogesterone	9	>20
Didrogesterone + mestranol	4	>10

*From Swyer and Little: J. Reprod. Fertil. Suppl. 5, 63, 1968. The nomenclature in the original has been retained.

Table II. Postponement of menstruation assay on Norgestrel*

Dose (mg.)	*No. of subjects*	*Response*		
		Positive	*Negative*	*% positive*
8	1	1	0	100
4	11	5	6	45
2	13	4	9	31
1	3	1	2	33
		ED_{50} 4 mg. (no. of observations 28)		
2 + 0.1 mestranol	10	10	0	100
1 + 0.1 mestranol	14	14	0	100
0.5 + 0.1 mestranol	13	11	2	85
0.25 + 0.1 mestranol	17	13	4	76.5
0.2 + 0.1 mestranol	2	2	0	—
0.125 + 0.1 mestranol	11	6	5	55
0.1 + 0.1 mestranol	3	0	3	0
		ED_{50} 0.125 mg. (no. of observations 70)		

*From Swyer and Little: J. Reprod. Fertil. Suppl. 5, 63, 1968.

in no position to assume qualitative identity among the compounds tested by Swyer and Little.[4] (All discussions on the Swyer-Greenblatt test will be based upon data published by Gerald Swyer and his associate Valerie Little; other people have employed the test differently than they and, therefore, the data are not comparable for comparative potency evaluations.) Within the limitations of the test, too few data are available to determine whether slopes are nonparallel. However, despite the reservation, this is the only available, critical pharmacologic method for comparing the human potency of progestogens on the endometrium. We reproduce here as Table I a listing of progestational agents as evaluated by Swyer and Little.[4] Although the results could be manipulated in several ways, they show that the potencies of the progestogens vary considerably and that the addition of an estrogen alters the "progestational" potency. In most cases this alteration is an increase in potency, i.e., a decrease in the ED_{50} of a compound when estrogen is added. Unfortunately, these data are not entirely self-consistent and not infrequently inadequate data are available to allow a satisfactory evaluation of potency. The addition of 0.1 mg. of mestranol is not always followed by a similar increase in potency of the progestogen. For example, norethynodrel appears to have an approximate ED_{50} of

Table III. Potency comparisons in various tests for estradiol-17β, 18-homoestradiol, and "propyl" estradiol*

	Vaginal smears			*% potency uterine growth*				
	Rat			*Rat*				
Compound	*1 day*	*2 day*	*Mouse*	*3 day*	*7 day*	*Mouse*	*Vaginal opening*	*Oviduct growth*
Estradiol-17β	100	100	100	100	100	100	100	100
18-Homoestradiol	30	1	1.25	?	67	<0.1	10	<100
"Propyl" estradiol	30	0.5	0.33	1.8	4.8	<0.1	3	<<100

*From Edgren, Jones, and Peterson: Eur. J. Steroids 2: 19, 1967, published by S. Karger AG, Basel.

about 20 mg. by itself; the addition of mestranol decreases this to 5.3 mg., a fourfold increase in potency. In contrast, Table II shows the ED_{50} for norgestrel alone to approximate 4 mg.; when the estrogen is added this dose decreases to about 0.125 mg., a 30-fold increase in potency.

These data immediately suggest that we are defeated. One cannot make potency evaluations for the available *combination* contraceptives even if one could assign meaningful evaluations of potencies for the progestational component alone.

Another possible measure of the activity of the progestational agents alone is the dose that has been employed for contraception in mini-pills; since the mini-pill contains no added estrogen, whatever is measured must be the progestational agent. (Personally, we do not feel that a "progestational" effect is being measured unless that word be redefined.) Norgestrel is the most potent known agent, with a mini-pill dose of 75 μg for the racemate and 30 μg for the *d*-enantiomorph. Norethindrone is about 10 times less potent than norgestrel in this regard, the mini-pill dose being 350 μg. This does not correlate well with the Swyer-Greenblatt test in which norgestrel is approximately equipotent with norethindrone, according to Swyer and Little. Megestrol acetate, once employed as a 500 μg mini-pill, was not significantly active in the delay-of-menses test. When combined with mestranol, *d*-norgestrel was 28 times more potent than megestrol acetate versus 17 for the mini-pill dosage. All of these attempted correlations *assume* parallel dose-response curves.

The situation is simple: there is no acceptable way to make a scientifically satisfactory series of potency estimates of progestational agents *per se*.

Estrogenic potencies

Estrogenicity is the next problem. For years most endocrinologists have considered mestranol to be less potent as an estrogenic agent than ethinyl estradiol. Since all commercial combinations contain either ethinyl estradiol or mestranol, other estrogenic agents may be ignored. Recently, Goldzieher and his associates[5] have suggested that mestranol is more potent than ethinyl estradiol in the inhibition of ovulation in human beings. This might relate to peculiar results in the hemicastrated rat where mestranol produced a greater depression of compensatory ovarian hypertrophy than was seen with ethinyl estradiol.[6] In contradistinction, most animal studies show mestranol to be less potent than ethinyl estradiol. In a conventional vaginal smear test in spayed female mice, mestranol had approximately 50 per cent the potency of ethinyl estradiol.[6] Mouse uterine growth studies showed that mestranol had approximately one twentieth the potency of Ethinyl estradiol.[6] More recently Jones and Edgren[7] showed that mestranol had approximately 50 per cent the potency of ethinyl estradiol, using vaginal keratinization in spayed rats as an end-point. The 95 per cent confidence levels overlapped between mestranol and ethinyl estradiol; however, the data indicated that mestranol was the less potent of the two. Uterine weights in the same study indicated that mestranol was less potent than ethinyl estradiol.

Therefore, with respect just to the two estrogens, we have an unanswerable question as to how prediction of clinical potency can be accomplished.

Another problem that impinges at this point is that of the broad discrepancies between estrogenic potencies as evaluated in varying testing procedures. This is clearly demonstrated in a paper discussing the potencies of various estradiol derivatives.[8] Eight separate testing procedures were employed to compare the effects of estradiol-17β and two of its homologues. These tests involved rats, mice, and chicks. Rat studies included vaginal smears (1 and 3 day testing procedures), uterine growth (3 and 7 day procedures), and vaginal opening; the mouse studies included vaginal smears and uterine growth; and in chicks oviduct growth was examined. The disparities in results are indicated repeatedly (Table III). In the rat vaginal smear assay (2 day test), 18-homoestradiol has approximately 1 per cent of the potency of estradiol, whereas in a single-administration testing procedure, the same

Table IVA. Dose required to produce vaginal keratinization in 50 per cent of rats*

Compound	*ED_{50} (μg)*	*95% confidence limits (μg)*
Ethinyl estradiol	4.9	3.3-10.0
Mestranol	9.4	5.8-18.3
Lynestrenol	191.6	2.3-435.9
Norethynodrel	234.9	133.4-651.3
Norethindrone acetate	573.0	267.0-1,681.9
Ethynodiol diacetate	1,342	671.3-10,935.4
Norethindrone	1,944.0	123.0-3,548.0
Methyltestosterone	>3,000.0	
Hydrocortisone	>3,000.0	
Progesterone	>10,000.0	
Norgestrel	>10,000.0	

*From Jones and Edgren: Fertil. Steril. 24: 284, 1973.

Table IVB. Estrogenic potency of various steroids relative to ethinyl estradiol*

Compound	*Potency (%)*	*95% confidence limits*
Ethinyl estradiol	100.0	
Mestranol	52.1	0.2724-1.0585
Lynestrenol	2.6	0.0112-0.0881
Norethynodrel	2.1	0.0100-0.0455
Norethindrone acetate	0.9	0.0043-0.0223
Ethynodiol diacetate	0.4	0.0016-0.0088
Norethindrone	0.3	0.0013-0.0053
Methyltestosterone	0.0	
Hydrocortisone	0.0	
Progesterone	0.0	
Norgestrel	0.0	

*Corrected—from Jones and Edgren: Fertil. Steril. 24: 284, 1973.

compound has almost one third the potency of estradiol. In the mouse uterine growth test, the potency for 18-homoestradiol is 0.1 per cent of the potency of estradiol-17β; in the vaginal opening test the compound has 10 per cent of the potency of estradiol.

The implication is clear from these data: no single testing procedure gives a series of potencies for the estrogens that is necessarily consistent with other tests and the potency evaluations will vary greatly from tissue to tissue, organ to organ, and species to species. *Therefore, one must look specifically at the target one wishes to evaluate.* With respect to thromboembolism, we do not think that the fact that mestranol is less or more potent than ethinyl estradiol in a pituitary blocking or a uterine growth test has any relevance to the alleged potential of the compounds to produce thromboses. Thus, thromboembolic phenomena must be considered as a separate entity, unrelated to other measures of estrogenicity, until correlations have been demonstrated. *However, the direct induction of experimental thrombosis by estrogens has not been reported.*

In addition to this confusion relative to the potency of the estrogenic component of the oral contraceptives is the problem of the estrogenic contribution of the progestational agent. Recently a series of studies was published on a broad range of progestational agents and other steroids that produce vaginal keratinization in rats when administered by the oral route.[7] Since uterine growth can be stimulated by progesterone, testosterone, and a broad range of other steroids, it is not specific and should not be considered as an "estrogenic" response. The vaginal effects, however, appear specific. Ethinyl estradiol, the standard, was the most potent steroid of the series studied, and all progestogens were weakly active, with the exception of progesterone and norgestrel (Table IV). These data may suggest conversion of the progestogen to an estrogen in vivo.

However, how does one employ these data? How does one come to a rational evaluation of the "estrogenicity" of a contraceptive agent? Does one add to the estrogenic content a percentage of the progestogen that may convert to estrogen or have estrogenic activities? For example, if we take the Lo-Estrin 1/20 combination, this material contains 20 μg of ethinyl estradiol as the estrogen. It also contains 1,000 μg of norethindrone acetate. According to the potency estimates in Table IV, norethindrone acetate has 0.9 per cent (call it 1 per cent for the sake of the argument) of the potency of ethinyl estradiol. One per cent of 1 mg. is 10 μg. Therefore, is the combination norethindrone acetate plus ethinyl estradiol in the 1/20 combination the clinical equivalent of giving 30 μg of ethinyl estradiol? When one adds mestranol to this, the confusion continues. Enovid-E contains mestranol as the basic estrogen in a dose of 100 μg. This is, according to Table IV, the equivalent of approximately 50 μg of ethinyl estradiol. Norethynodrel has approximately 2 per cent of the potency of ethinyl estradiol, so the norethynodrel, 2.5 mg. in Enovid-E, would be the equivalent of 50 μg of ethinyl estradiol. Therefore, is the combination Enovid-E the clinical equivalent of giving 100 μg of ethinyl estradiol? The answer to these two questions regarding Lo-Estrin and Enovid-E is, certainly, "No."

But, of course, the exercises in the preceding paragraph presuppose that rat vaginal studies project to clinical effects. It would appear that this is not true from Goldzieher's observations on human pituitary blockade.

It should be evident at this point that it is not possible to make a meaningful evaluation of the estrogenic contributions of either the estrogen itself or the

Table V. Antiestrogenic effects of various steroids*

Steroid	Mouse vaginal smear	Uterine growth	
		Antiestrone	Antiestriol
Standard:			
Progesterone	100S†	100S	I
Testosterone	200	20	A
Estrone	I	I	I
Acetoxyprogesterone derivatives:			
Medroxyprogesterone acetate	A	290	—
Chlormadinone acetate	130	a	—
Megestrol acetate	—	60	—
Nortestosterones:			
Norethindrone	730	800	A
Norgestrel	7,400	>3,300	A
Norethynodrel	I	I	I
Ethynodiol diacetate	—	a	—

*From Edgren, Jones, and Peterson: Fertil. Steril. 18: 238, 1967.
†Key to symbols; A = active; a = active, literature report; I = inactive; S = standard.

Table VI. Potencies of progestogens*

Steroid	Potency		
	Progestational (%)	Antiestrogenic (%)	Contraceptive dose/day† (μg)
Progesterone	100	100	
Chlormadinone	3,500	130	500
Norethisterone	8	730	350
Norgestrel (Racemate)	915	7,400	75

*From Edgren: J. Reprod. Med. 2: 79, 1974.
†For Pearl index of 2 to 3 in large-scale studies of progestogens as mini-pills.

progestational component to the effects of a given combination on a specific end-point of estrogenic action. It would seem that each product will have to be considered on its own merits and its effects restricted to only one end-point of action.

Antiestrogenic action

Further difficulty arises from the interaction of the progestogen with the estrogen. Most of the progestational agents commonly used as components of oral contraceptives are estrogen antagonists, but the meaning of this at a biochemical level has not been clearly defined. Biologically, it is abundantly clear that the administration of an estrogen is followed by certain biologic effects, apparently in all species of mammals. The most clearly defined are uterine growth, vaginal cornification, and pituitary blockade. The first two, the uterine growth and the vaginal changes, may be reversed by the simultaneous administration of certain compounds, notably the progestational agents that are being considered here. On the other hand, studies on hemicastrated rats, which are believed to measure the blockade of the pituitary, do not indicate an antiestrogenic effect. Further, the Ramirez-McCann rat, employed for the measurement of luteinizing hormone–releasing factor, requires large doses of both estradiol and progesterone to block totally the release of gonadotropins; if progesterone were blocking the effect of the estrogen it would cause release of the luteinizing hormone and the preparation would not be suitable for this type of assay. In contradistinction, Goldzieher seemed to believe that the progestational agent will potentiate the effect of the estrogen in women. Therefore, we must be highly specific and define the target that we are considering before any potency evaluation that might be meaningful can be attempted.

The antiestrogenic potencies of a number of progestational agents have been evaluated with standardized testing procedures (Table V). The antiestrogenic potencies appear to relate closely to the mini-pill contraceptive doese (Table VI). However, we see no way of merging these data for clinical purposes.

An example

It would be desirable if one could evolve an "estrogenic index" for these materials that would add to the estrogen component itself the estrogenic con-

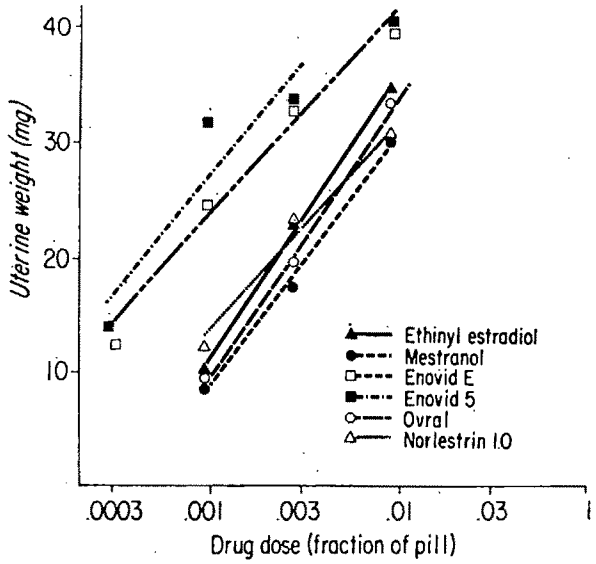


Fig. 1. Oral contraceptives with linear regression lines parallel to that of ethinyl estradiol. (From Chihal, Peppler, and Dickey: Am. J. Obstet. Gynecol. 121: 77, 1975.)

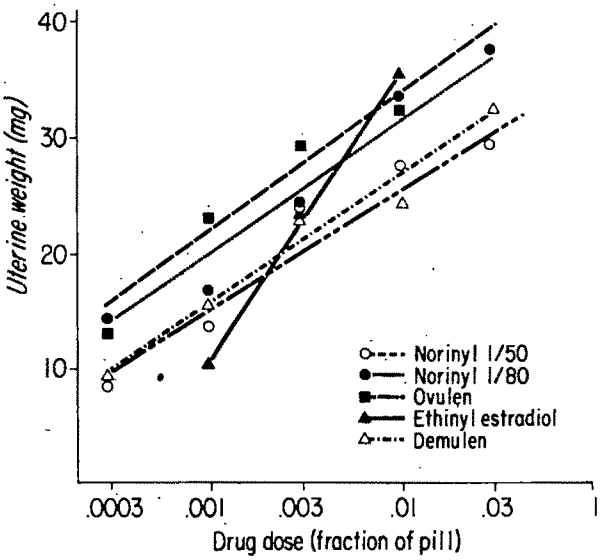


Fig. 2. Oral contraceptives with linear regression lines parallel to that of Norinyl-1 + 50. (From Chihal, Peppler, and Dickey: Am. J. Obstet. Gynecol. 121: 77, 1975.)

tribution of the progestational component and subtract the antiestrogenic effect of the progestogen. This is not possible. Evaluations of these materials will have to be based on their own merits.

It would seem to us that the only meaingful approach to a comparative study of oral contraceptives and stroke or thomboembolic phenomena, cancer, or any other untoward condition that might be associated with the use of a given product would have to be based on logistic, life table, or incidence data on the specific

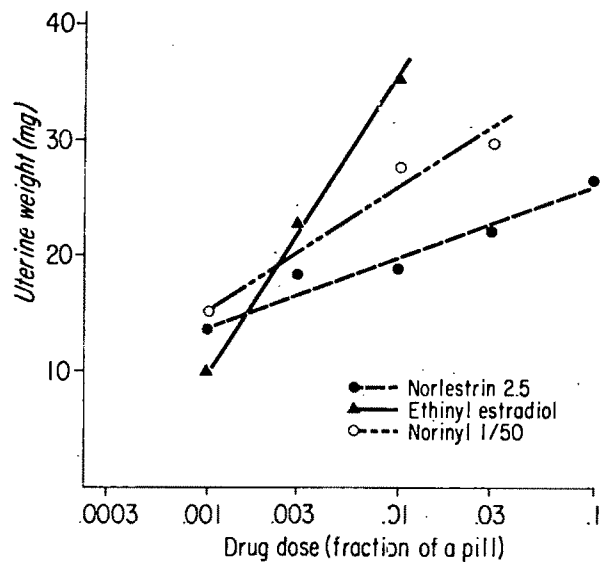


Fig. 3. Oral contraceptives with linear regression lines not parallel to that of either ethinyl estradiol or Norinyl-1 + 50. (From Chihal, Peppler, and Dickey: Am. J. Obstet. Gynecol. 121: 77, 1975.)

condition under consideration. A preconceived, established rating of estrogenicity or progestational potency cannot contribute meaingfully.

Various workers have made efforts to evaluate oral contraceptives in terms of relative "estrogenicity," relative progestational "dominance," etc. These evaluations are more wishful thinking than science. However, few clinicians would deny that the over-all clinical effect of Enovid, for example, is folliculoid, whereas that of a norgestrel- or norethindrone-containing contraceptive appears to be primarily progestational and/or androgenic. However, such generalization from clinical impression is a poor solution to our problem.

Recently, an attempt was made to compare oral contraceptives for their "estrogenic" potencies.[10] The broad conclusions reached are untenable for the following reasons. First, these workers used mouse uterine weights for definition and evaluation of estrogenic effects. The uteri of rats and mice respond to progestational agents and androgens, as well as to estrogens. Therefore, the uterine growth response is not specific, does not necessitate that a compound is estrogenic in the usual sense, and could therefore be misleading. Second, the authors' methods are questionable: they bought commercial preparations and the tablets were ground up to form slurries, which were then administered orally to mice. Ten tablets were pooled to form the initial samples and final amounts were dilutions of these initial slurries. We cannot believe that accurate dilutions are possible in these circumstances. Third, each mouse received massive

amounts of excipients, binders, bulk materials, etc., relative to the steroids that it received. Fourth, in a highly sensitive assay of activity, slight deviations in the original tablets, which are within tolerable limits for human use, could produce gross errors in the animal study. Fifth, the ethinyl estradiol and mestranol were obtained from sequential tablets; therefore, the ratios of extraneous to steroidal materials was greater for these tablets and less for the combination tablets.

The results of this study[10] are displayed in Figs. 1 to 3, which show two sets of dose-response curves with regard to slope. The data suggest that the Enovid combinations, Ovral and Norlestrin (1 mg.) show dose-response curves that are parallel to ethinyl estradiol and mestranol, while Norinyl 1/50, Norinyl 1/80, Ovulen and Demulen show dose-response curves that are different from their estrogenic components. One combination, Norlestrin 2.5, had a slope that was parallel to neither of these two major groups. The first conclusion one reaches is that potency relationships among the groups cannot be drawn in any meaningful fashion; whereas it is possible to evaluate the potency of Enovid-E, Enovid-5, Ovral, or Norlestrin in terms of ethinyl estradiol or mestranol, deriving potency estimates for Norinyl 1/50, Norinyl 1/80, Ovulen, Demulen, or Norlestrin 2.5 in terms of either of the standard estrogens is meaningless. Further, drawing a relationship between the two Enovid products, for example, and Demulen would be ridiculous.

One over-all problem in this type of analysis is inherent in the data of Figs. 2 and 3. Here are two groups of compounds with dose-response curve slopes more shallow than that of the standard. The data suggest that at lower doses the uterotropic action of the progestational agents may synergize with the uterotropic activity of the estrogen, whereas the antiestrogenic effect of the progestogen is apparent at the higher doses. This kind of interaction was common in a number of our (R. A. E.) early studies involving the interactions of androgens, progestogens, or corticoids with estrogens. However (and here is the critical point as far as we are concerned), where on the curve do human beings fall? If one of these materials be given to a woman, does she fall on the curve at the lower level where the compounds may synergize or does she fall on the curve at the higher dose levels where the progestogens appear to inhibit the estrogen? In our opinion, this study[10] is really not relevant to the estrogenicity of contraceptives in human subjects.

Conclusions

We do not feel that it is currently scientifically possible to answer the question of oral contraceptive "potency," nor do we believe that a solution would provide clinically meaningful answers. No laboratory or clinical measure of "potency" will predict specific side effects with useful precision, except, of course, data based upon the side effect itself. While this statement holds for the component, estrogen and progestogen, it is ever more valid with respect to the combination. One cannot ignore the mutual interactions of the progestational and estrogenic components, ignore the complications of varying estrogen/progestogen ratios, and then extrapolate from an organ or biochemical response in laboratory animals or human beings to a clinical situation (e.g., thromboembolism incidence) that is not itself observable directly, that is not demonstrable experimentally, and that is posited solely upon the basis of retrospection,* voluntary physician reporting, and sales figures.[11] Such reasoning has led to governmental action against oral contraceptives containing more than 50 μg of "estrogen" in Great Britain and Sweden. Qualified recognition was accorded by the FDA.[12] While these actions may perhaps be supported as efforts to err on the "safe side," the basic data do not meet the test of scientific validity and, further, spurious incorporation of "potency" data will not solve the immediate problem, i.e., the evaluation of safety of the oral contraceptives for their users.

*Dr. Richard P. Dickey, who disagrees with the thesis presented here, has kindly pointed out that we deal summarily with the prospective studies of the Royal College.[1] This is not our intention. Some months ago, in a detailed reanalysis of the data in the Royal College report, one of us (F. M. S.) noted that the evaluation of the grand totals on reported morbidity (Table 13.2, p. 85, of reference 1) did not exclude predisposing factors in the evaluation of the standardized rate and that this table provided the denominator for estimated incidences of idiopathic venous thrombosis listed in tables 7.3 (p. 45) and 7.5 (p. 46). This point was called to the attention of Dr. Clifford Kay, Chairman of the Executive Committee of the Oral Contraception Study of the Royal College. Dr. Kay, in a letter to *Lancet* (June 21, 1975, p. 1381), has now corrected and updated Table 7.3; however, the original Table 7.5 still reflects cases of idiopathic thrombosis per woman-years contributed by women with and without predisposing conditions, and still refers to different estrogens combined with varying amounts of different progestogens. Thus, in our opinion, Table 7.5 cannot be interpreted as demonstrating any dose-response relationship between "estrogens" and thrombosis.

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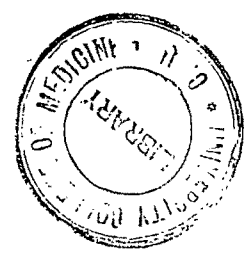
Intrauterine Asphyxia in the Developing Fetal Brain

"Intrauterine Asphyxia in the Developing Fetal Brain," a symposium, co-sponsored by the Department of Pediatrics, University of California, San Diego, California, and the Institute for Pediatric Service of the Johnson & Johnson Baby Products Company, will be held at the Town and Country Hotel, San Diego, September 9-12, 1976. The Chairman is Louis Gluck, M.D. An international faculty of neonatologists, pediatricians, obstetricians, and other specialists will discuss the important aspects of intrauterine asphyxia as it affects the developing fetal brain. For further information, write: Steven Sawchuk, M.D., 501 George St., New Brunswick, New Jersey 08903.

GYNECOLOGY

Spring clip sterilization: One-year follow-up of 1,079 cases

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This is a report of 1,079 patients who underwent laparoscopic clip sterilization as of March, 1974. A one-year follow-up was obtained on 977 patients, or 90.5 per cent. Complications due to the clip technique appear limited to postoperative cramps for 24 to 48 hours in 26 per cent of patients. No ectopic pregnancies were detected. Pregnancies, when corrected for unsuspected existing pregnancies and surgical and manufacturing errors, occurred in 2 to 6 cases, for a method failure rate of 2 to 6/1,000. This report documents that experienced laparoscopists can perform this practice with local anesthesia, in combination with first-trimester abortion, and in hospital facilities other than an operating room.

EFFORTS TO DEVELOP simpler, safer, and more reversible methods of female sterilization led to the development of a clip that could be applied by laparoscopy and would occlude the tube by compression with a metal spring.[1] In September, 1972, clinical trials were begun,[2] and by March, 1973, over 1,000 patients had undergone this procedure. Details of the development of this program have been reported elsewhere,[3, 4] and the six-month follow-up data also have been presented.[5] The purpose of this paper is to present the final report of this study, describing complications and pregnancies experienced after one year of follow-up (see Table I).

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Table I. Collaborative sites

Location	*Sterilizations as of March, 1974*	*One-year follow-up*
Chapel Hill, North Carolina	429	375
Los Angeles, California	31	26
Fort Worth, Texas	36	32
Ann Arbor, Michigan	15	10
London, England	106	93
San Salvador, El Salvador	137	128
Bombay, India	105	100*
Bangkok, Thailand	113	113
Singapore	107	100*
Total	1,079	977

*Approximate.

Table II. Medications used with local anesthesia

Local anesthesia: Xylocaine plus*	*No. performed*
No medication	14
0.1 mg. of fentanyl	120
0.1 mg. of fentanyl + 5 to 10 mg. of Valium†	340
50 mg. of Demerol ‡ + 50 mg. of Phenergan§	380
Combined with abortion	166

*Astra Pharm. Products, Inc., 7 Neponset St., Worcester, Massachusetts 01606.

†Roche Labs., Div. Hoffman-La Roche Inc., Roche Park, Nutley, New Jersey 07110.

‡Winthrop Labs., Div. of Sterling Drug Inc., 90 Park Ave., New York, New York 10016.

§Wyeth Labs., Div. American Home Products Corp., P. O. Box 8299, Philadelphia, Pennsylvania 19101.

Methods

Anesthesia. All but five of the procedures in Chapel Hill were performed with minimal local anesthesia. More sedation and local anesthesia were used in Bangkok, Bombay, and El Salvador. A mixture of local and general techniques were used in Los Angeles, Forth Worth, Ann Arbor, and London. Excellent general anesthesia was available and used in Singapore. A summary of the medications used with local anesthesia is given in Table II.

Sterilizations performed following abortion. All spring clip applications in Bombay were in combination with first-trimester abortion. At Chapel Hill, 41 were done at the time of first-trimester abortion, and eight were done after second-trimester abortion. Twelve were done in England after first-trimester abortion.

Facilities. In the centers of three collaborators, facilities other than a standard, fully equipped operating room were used: At Chapel Hill, over 100 of the patients were sterilized in the Clinical Research Unit, a facility in the hospital consisting of a bedroom with reclining chairs as recovery facilities. An additional 40 patients, not of this series, have since been sterilized in our clinic treatment room. In El Salvador, a room in a family planning clinic quite removed from a hospital has been used for several thousand sterilizations, including the clip technique reported here. In Bombay, all sterilizations reported were performed in a clinic primarily utilized for abortions, again removed from a hospital. Complications in these settings were minimal, although it must be emphasized that very experienced laparoscopists were performing these procedures in these settings.

Patient selection. All patients inquiring about sterilization at Chapel Hill were offered the clip as an experimental alternative with a promise of interrupting pregnancy in the first trimester without charge should a failure occur. No patients were turned down because of obesity or recent pregnancy; only one patient was rejected because of previous pelvic surgery (multiple abdominal scars and a functioning colostomy from diverticulosis). There were no prescribed medical contraindications in the other centers, to the author's knowledge. Therefore, this report represents a series selected by patient volunteering only with no medical selection.

Results

Operative time. Table III presents the ranges of operative and recovery times experienced in those centers that had developed this technique into an outpatient procedure with the use of local anesthesia. Room turnover time (time required from start to finish of a series of cases in one room) is a sensitive measure of both the doctor's true surgical speed and the efficiency of his operating team.

Complications. *Due to laparoscopy.* One laparotomy was required because of a retroperitoneal hematoma caused by grazing of the sacrum by the Verres needle. The hematoma was self-limiting; it was observed and no further operation was required.

One death was due to massive myocardial infarction in a patient with artificial mitral and aortic valves after a delayed abdominal wall hemorrhage forced the discontinuation of anticoagulation therapy. At autopsy, the sites of clip application were intact.

Due to prototype equipment. Optic fogging was a constant bother and was partly due to the design of the

prototype equipment. Deviations from specifications in the manufacturing process led to failure of an applicator to free itself of the clip in several centers and required laparotomy in one, reapplication of another clip to stop tubal oozing after stretching in four cases, and coagulation to stop the oozing in two cases. The manufacturing defects have been identified and eliminated in the "third generation" manufacturing designs.

Due to the clip. Pain at the time of clip application was noted early in the study; therefore, a technique of anesthetizing the tube was devised.[6] Local anesthesia is transient, and 6 to 26 per cent of the patients with light sedation experienced postoperative cramping similar to that of a menstrual period. Also noted with light sedation was a vagal reflex characterized subjectively by nausea, clamminess, and faintness and objectively by bradycardia and hypotension. These symptoms responded promptly to atropine and were noted less frequently with antihistaminics only as medication.

A summary of complications experienced is given in Table IV. There were no bowel burns or injuries.

Pregnancies. Table V summarizes pregnancies and the reasons for failure of the sterilization method in this study. An over-all crude failure rate of 25/1,000 in the initial cases is analyzed below.

Due to surgical error. Three patients were pregnant at the time of clipping and subsequently were delivered or aborted. In the first six months of the study, clips were placed on the distal, or ampullary, portion of the tube, and it was found that the clip would not reach across this portion of the tube, with resulting pregnancy. Therefore, instructions to the collaborators emphasized placing clips on the proximal, or isthmic, portion only.

New optics, partial obstruction of the visual field by the clip-applying apparatus, and fogging contributed to application of the clip onto structures other than the tube, such as the round ligament and varicosities of the broad ligament, and to incomplete isthmic application. Anatomic difficulties were encountered in some obese women and with recently midtrimester abortion which made application of the clip onto the tube impossible in two women because of the combination of obesity, an enlarged uterus, and tubal edema.

Due to manufacturing error. The springs were specified to have 75 Gm. of pressure at the ends of the spring, but a number of springs well below these specifications were distributed during the early months of 1974. This manufacturing error was detected in August, 1974, and all clips were promptly recalled. Women who became pregnant at Chapel Hill in whom the clip appeared to be well applied to the isthmic portion of the tube underwent electrocoagulation removal of the clips with the Soderstrom snare technique or by simple coagulation and excision. Testing of four of these springs in the laboratory revealed tensions well below the minimum 75 Gm. in three. The current manufacturer of these springs has improved the tension to well above this minimum level.

Correct application of good springs. Two pregnancies have been documented which occurred with proper application of clips with good springs. In one, a clip applied close to the uterus had not been covered with epithelium, but rather the tubal endothelium had grown around the clip and had created a passage for sperm and egg open to the peritoneum. In the second, dye insufflation and serial sections of the removed clips

Table III. Average operative and recovery times

Operation	15-18 minutes
Room turnover	15-30 minutes
Recovery	3-5 hours
Hospital stay	4-8 hours

Table IV. Complications

Complication	*No.*
Laparotomy	
Malfunction of applicator	1
Verres needle hematoma	1
Other	
Tubal tear due to applicator malfunction (corrected by second clip)	4
Wound discharge	6
Postoperative vagal reflex	2-8%
Postoperative cramps	4-26%
Bowel burns or injury	0

Table V. Pregnancies

Pregnancies	*No.*
Ectopic	0
Pregnant at operation	3
Ampullary application	6*
Application to structure other than tube	5*
Poor isthmic application	2*
Weak spring	3*
Unknown	4*†‡
Correct application, good spring	2†
Total	25§

*Surgical or manufacturing error.

†Method failure rate (2 to 6/1,000).

‡One delivered—to undergo repeat laparoscopy; one aborted—vasectomy chosen; two from Singapore and Bombay—no data.

§Crude failure rate.

failed to reveal any passage for sperm and egg to unite and implant in the uterus; the explanation of this failure is unknown.

Ectopic pregnancies. To date, no ectopic pregnancies subsequent to clip application have been detected.

Unknown causes of failure. Two women became pregnant and have not been studied further to date; one woman is currently deciding between repeat laparoscopy and hysterectomy by her private physician after a normal delivery, and one woman declined laparoscopy after abortion because she preferred that her husband undergo vasectomy. Two patients overseas have become pregnant with no additional information available.

Method failure rate. Two pregnancies occurred when good clips were properly applied to the isthmic portion of the tube. Four pregnancies occurred which could have been due to surgical error or manufacturing error, but the actual cause is unknown. Other pregnancies occurred due to documented surgical or manufacturing error. When pregnancies known to be due to such errors are excluded, there is a method failure rate of 2 to 6 per 1,000 cases after one year of application.

Comment

Minimizing problems. This report presents all the complications and pregnancies experienced with a new technique of laparoscopic sterilization with the use of prototype equipment in a wide variety of clinical settings and with no established contraindications. Thus, the problems and failures in this first report, as in any other first report, should be the highest possible. We learned that these problems can be minimized by certain precautions.

Proper teaching. The fixed optics can disorient a physician used to keeping his distance from the field as the instrument is brought close to the tube for clip application. Also, the clip must be pressed into the isthmic portion of the tube and mesosalpinx, in contrast to the electrocoagulation technique where the ampullary portion of the tube can be lifted away. These changes in technique were learned the hard way and account for about half of the pregnancies in this series. Now that this change in technique is known to be necessary, proper teaching, through manuals distributed with the instrument or preferably by direct demonstration in patients, should eliminate the main cause for method failures in this series.

Equipment. As in any developmental engineering work, prototype equipment demonstrates problems unanticipated by the best a priori thinking efforts and leads to improvements in design based on field experience toward "third-generation" applicators and clips which have been redesigned as a result of these problems and are now suitable for manufacture.* A two-puncture technique, now under evaluation here and overseas, may also solve problems of visualization and application.†

Contraindications. This study was designed to elicit contraindications by seeing where failures would occur.

ANXIETY. Though almost all patients in the series could have been sterilized with local anesthesia, occasional patients with a low pain threshold or high anxiety level, in retrospect, would have done better with more anesthesia. This can best be elicited by the pelvic examination: If marked muscle rigidity or discomfort is noted, general anesthesia should be planned. To avoid the bradycardia and hypotension due to vagal reflex, atropine premedication is also recommended.

OBESITY. Obesity was *not* a contraindication but turned out to be a relative indication when sterilization was desired compared to the alternatives.

ADHESIONS. These were relative contraindications. Adhesions between the isthmus and bowel resulted in failure to visualize the isthmic portion of the tube in two patients, with subsequent pregnancies. Other adhesions were no hazard during clip application but could have been if coagulating current had been applied.

MIDTRIMESTER ABORTION. This was a real contraindication. If the patient was obese and had a large (boggy) uterus, visualization of the tube for clip application with local or general anesthesia was found to be very difficult.

CHRONIC PELVIC PAIN OR MARKEDLY IRREGULAR MENSES. Although these did not interfere with clip application per se, they can develop into problems of management after any form of sterilization and may better be managed by hysterectomy in the long-term interests of the patient desiring no more children.

When is the experiment over? In this era of careful regard for patients' rights and absence of legislative regulation of the evaluation of surgical equipment, a new policy had to be evolved in regard to deciding when this experiment was concluded. If a sterilization technique is biologically inadequate, it will be detected quickly, within the first year of study.[8] If a procedure appears to be adequate, a number of patients need to be followed to allow a comparison of effectiveness with "standard" techniques of coagulation and division. Random-assignment comparative studies of clip versus coagulation techniques are in progress, and prelimi-

*Richard Wolf Manufacturing Corp., Rosemont, Illinois.
†Rocket of London, Ltd., London England.

nary results have been presented.[9, 10] Such studies will properly compare these sterilization techniques. Long-range studies of such large numbers of patients, though desirable, are impossible in our mobile society where at least 5 to 10 per cent of patients simply disappear to follow-up annually, making difficult interpretation of long-range incomplete data.

With these considerations in mind, a one-year positive contact follow-up of over 90 per cent of 1,000 patients seemed to be a reasonable compromise between what is desirable and what is possible. Public presentation of these data (at the meeting of the American College of Obstetricians and Gynecologists in May, 1975) constituted the fulfillment of the scientific purpose of the "experimental" portion of this study. We no longer ask for consent for human investigation from our patients for insertion of the clip.

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What's New and Important in Ob-Gyn

A postgraduate symposium in obstetrics and gynecology entitled "What's New and Important in Ob-Gyn" will be presented October 12-16, 1976, in Dallas, Texas. It will include a review of expanded information in selected Ob-Gyn topics: Endocrinology of Reproduction, Patho-Physiology of Pregnancy, the Fetus, Gynecologic Oncology, and Gynecologic Pathology. Sponsors are the Department of Obstetrics and Gynecology of The University of Texas Health Science Center and Southwestern Medical School at Dallas, Parkland Memorial Hospital, and the A. Webb Roberts Center for Continuing Education. For information, write: Daniel E. Scott, M.D., Program Coordinator, Department of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Texas 75235.

Cyclic changes of cervical mucus enzymes related to the time of ovulation

I. Alkaline phosphatase

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The concentration of alkaline phosphatase in cervical mucus was serially determined during a menstrual cycle in five normal ovulatory women and correlated with the time of ovulation as monitored by the basal body temperature and radioimmunoassay of serum lutenizing hormone (LH), progesterone, and estradiol. The activity of alkaline phosphatase decreased significantly at midcycle just prior to the LH surge and began to rise after ovulation. Self-detection of cervical mucus alkaline phosphatase may provide a practical method of ovulation prediction.

DETECTION OF OVULATION is an integral part of the investigation of an infertile couple. A simple and accurate method of ovulation prediction would result in an improved method of natural family planning which is of considerable interest to millions of women who because of religious or moral reservations are reluctant to use mechanical or steroidal contraceptives.

Cyclic changes in various physical properties and biochemical constituents of cervical mucus are known to reflect accurately the hormonal changes associated with an ovulatory menstrual cycle and may be utilized clinically to determine the time of ovulation.[1]

It has been shown that there is a significant increase in the amount, crystallization, and spinnbarkeit properties and a marked decrease in viscosity and cell content of cervical mucus in the midcycle prior to ovulation and a reversal of these changes following ovulation and in the luteal phase. Among various constituents of cervical mucus, the concentrations of prealbumin, albumin, α_1-antitrypsin, transferrin, immunoglobulins G and A, and sialic acid decrease, whereas the relative percentage of mucin increases in the midcycle.[2]

The presence of several enzymes in human cervical mucus has been reported. These include alkaline phosphatase, acid phosphatase,[2, 3] amylase,[4] muramidase,[5] glucose phosphate isomerase,[6] and a fibrinolytic enzyme system.[7] In most previous studies, only random samples of cervical mucus were obtained or ovulation was determined by peripheral changes such as those in the basal body temperature (BBT). Hence, the precise relationship between enzyme changes and the time of ovulation could not be ascertained.

The purpose of this study was to determine the concentration of alkaline phosphatase in cervical mucus obtained serially during a menstrual cycle and to relate its activity to the time of ovulation reflected by the BBT and the assays of serum luteinizing hormone (LH), estradiol-17β (E_2), and progesterone.

Material and methods

Five normal ovulatory women between the ages of 19 and 23 years (mean 20.4) were selected for study. Samples of blood were obtained from each woman every two days before cycle Day 10 and after Day 20 and daily in the midcycle (Days 10 to 20) during one

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menstrual cycle. Blood samples were collected by antecubital venipuncture, allowed to clot, refrigerated at 4° C. no longer than 24 hours, and then centrifuged. The serum was frozen and stored at −20° C. until assayed. LH, E_2, and progesterone levels were determined in each blood sample by radioimmunoassay with the techniques described by Midgely[8] and Abraham and associates,[9] respectively.

Samples of cervical mucus were obtained daily in the midcycle (Days 10 to 20) and every two days during the rest of the cycle. An unlubricated speculum was used, and the cervix was cleansed with dry cotton. Mucus was aspirated from the cervical canal with a tuberculin syringe (without needle). An attempt was made to collect the entire pool of mucus. When mucus could not be aspirated because of increased viscosity, it was removed with mucus forceps and transferred to a previously weighed tube. After weighing, the tube was sealed airtight, and the mucus was stored frozen at −20° C. until a series of samples representing a full menstrual cycle were collected. The frozen samples of a full cycle were thawed rapidly, and to each sample 1 ml. of distilled water was added. The mucus was carefully mixed with a small glass rod until completely dissolved in the water. The tubes were allowed to sit overnight at 4° C. and then were subjected to sonication* for one minute at 25 per cent maximum power. Sonication served to disrupt the mucin to the extent that quantitative transfers of the mucus could be made.

Alkaline phosphatase was assayed by a modification of the fluorometric procedure of Greenberg[10] with α-naphthyl-sodium-phosphate used as a substrate. The final concentration of substrate in the reaction mixture was 0.2 mM in a volume of 3.5 ml. Linear reaction rates were followed at 30° C. with a fluorometer coupled to a linear log recorder. Enzyme activities were expressed as nanomoles of naphthol released per minute per gram of wet weight of mucus. The amount of sonicated cervical mucus taken for analysis varied from 0.05 to 0.2 ml.

All laboratory assays were performed in duplicate. Average values of two determinations were recorded as the final result.

Statistical analysis of the results of hormonal assays, BBT, and cervical mucus alkaline phosphatase was done with the aid of a computer.

Results

All cycles were presumed to be ovulatory on the basis of biphasic BBT and LH, E_2, and progesterone assays.

*Sonicator, Bronwill Scientific, Inc., 1128 Lexington Ave., Rochester, New York 14607.

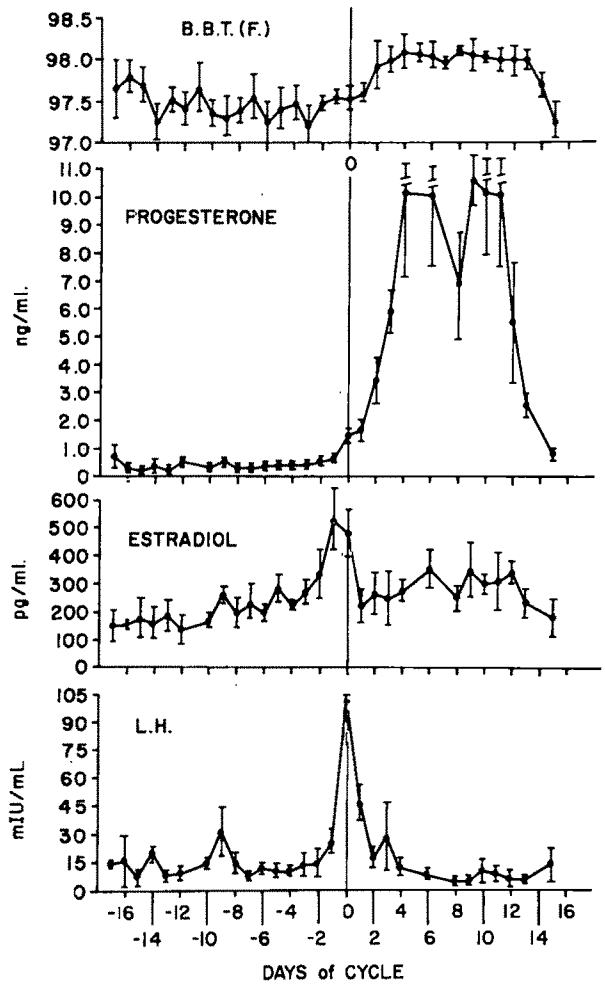


Fig. 1. Composite profile of mean serum LH, E_2, and progesterone and BBT throughout the menstrual cycle in five women. Day 0 = Day of LH peak. Vertical bars represent one standard error of the mean.

The mean length of the luteal phase of the cycles measured from the LH surge to the onset of the next menses was 14.6 days. Because of variation in cycle lengths, the data were analyzed and centered according to the day of the midcycle LH surge which served as the reference point and was designated as Day 0.

Hormonal pattern. Fig. 1 illustrates the mean (±standard error) daily concentration of serum LH, E_2, and progesterone in all five cycles studied. The levels of serum LH and progesterone and their patterns are similar to those previously reported.[1, 11] The preovulatory rise of serum progesterone[1] is again confirmed. Serum E_2 showed a gradual increase during the follicular phase, reaching a distinct and significant peak one day before the LH surge. After the LH peak, serum E_2 showed a precipitous decline followed by a steady rise to the midluteal phase and a subsequent

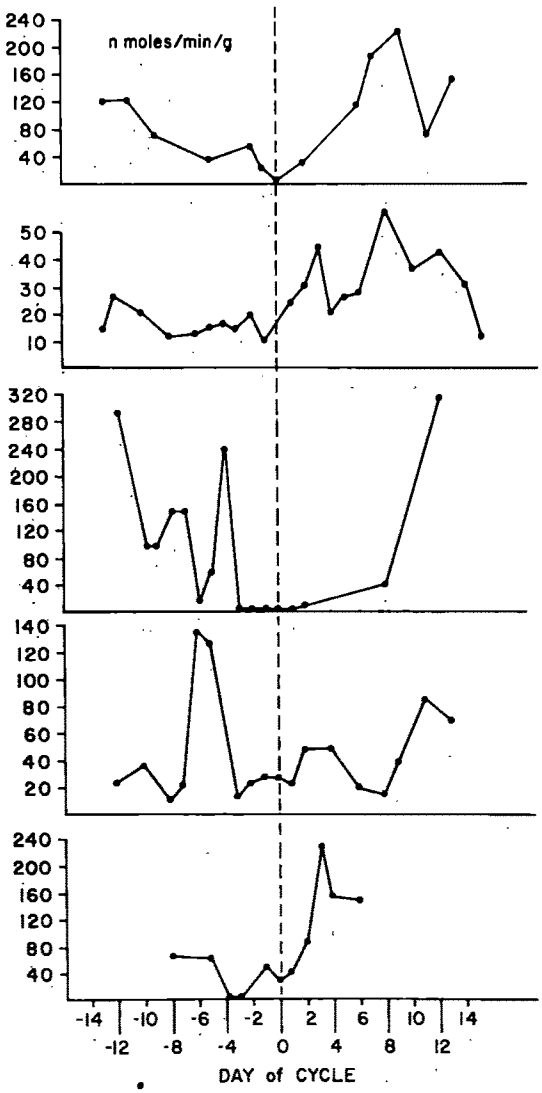


Fig. 2. Individual pattern of alkaline phosphatase concentration during one menstrual cycle in five subjects. Day 0 (vertical dotted line) = Day of LH peak seen in Fig. 1. Activity of the enzyme is expressed as nanomoles per minute per gram of wet weight of cervical mucus.

decrease prior to menstruation. Mean levels of E_2 were higher during the luteal phase than during the follicular phase and were significantly elevated in the midcycle compared to other phases.

BBT. Mean BBT was 97.6° ± 0.3° F. during the proliferative phase and 98.0° ± 0.1° F. in the luteal phase. The BBT began to rise simultaneously with the LH surge (Fig. 1). A significant rise did not occur until two days after the LH peak. The luteal phase increase in the BBT was also significant.

Cervical mucus alkaline phosphatase. Fig. 2 shows the pattern of alkaline phosphatase activity in individual cycles. The concentration of alkaline phosphatase decreased about three days before and began to rise two days after the LH peak.

Table I. Mean alkaline phosphatase levels (nanomoles per minute per gram) and ranks of the three phases of the menstrual cycle for each subject

	Phase I (follicular)		*Phase II (midcycle)*		*Phase III (luteal)*	
Subject	*Mean*	*Rank*	*Mean*	*Rank*	*Mean*	*Rank*
1	45.83	2	40.20	1	157.70	3
2	142.20	2	7.50	1	219.40	3
3	61.13	2	23.74	1	119.90	3
4	78.25	3	15.67	1	64.20	2
5	17.09	1	18.10	2	33.51	3
Sum	344.5	1	105.21	6	594.71	14
Mean	68.9	2	21.04	1.2	118.94	2.8

S = 6.4. P = 0.03.

To evaluate the significance of the midcycle (preovulatory) decrease of alkaline phosphatase, mean enzyme activity for each subject for different phases of the menstrual cycle was determined (Table I). The three phases of the menstrual cycle consisted of: (1) the follicular phase which began with the onset of menses through Day −4 (Day 0 = day of LH surge); (2) the midcycle (Day −3 to +1); and (3) the luteal phase (Day +2 to the onset of the next menses). Phase means for each subject were ranked (Table I) and evaluated with the Friedman rank sum statistic (S). This method is appropriate for a repeated-measures design.[12] The statistic

$$S = \frac{12}{nk(k+1)} \sum_{j=1}^{k} R_j^2 - 3n(k+1) = 6.4,$$

where Rj is the sum of n ranks for each of k treatments was computed.

With the use of tables based on the ranks of k = 3 items by n = 5 subjects,[13] the S statistic was found to be significant beyond the 5 per cent level of confidence (p = 0.03). Thus, the hypothesis that there are no differences among the three phases was rejected.

These analyses demonstrate a significant decrease of alkaline phosphatase activity in the preovulatory phase of the menstrual cycle.

Comment

The pattern of serum LH and progesterone observed in this study is identical with that previously reported. Serum E_2 patterns and levels are also similar to those reported by Mishell and colleagues,[11] Abra-

ham and associates,[14] and Korenman and Sherman.[15] The peak of serum estradiol in this study occurred one day prior to the LH surge in individual cycles and in the composite of all cycles.

Alkaline phosphatase has been detected by several investigators in cervical mucus; however, the precise cyclic change of this enzyme in relation to the time of ovulation has been controversial. Leeb and Ploberger[16] found an increase in alkaline phosphatase activity in cervical mucus before and a decrease after ovulation. Smith and co-workers[17] reported an elevation of mucus alkaline phosphatase concentration at or about the time of ovulation in normal patients and in those receiving human menopausal and chorionic gonadotropins for induction of ovulation. In their study, they did not use hormonal assays to determine the precise time of ovulation and they did not attempt to correlate enzyme activity with mucus volume or weight. Sobrero and associates[18] described an increase in alkaline phosphatase activity from two days before to one day after the day of ovulation as determined by a thermal shift. Gregoire and colleagues,[13] using random sampling, found no cyclic change in cervical mucus alkaline phosphatase activity during the menstrual cycle.

These contradictory results stem from imprecise methods of ovulation timing or the lack of serial sampling. In this study the activity of alkaline phosphatase was found to decrease significantly before and increase after ovulation. The pattern of enzymatic change has been observed for other enzymes, e.g., amylase[4] and muramidase.[5]

Currently, the site of production or the functional significance of cervical mucus alkaline phosphatase has not been identified. The preovulatory decrease of alkaline phosphatase may facilitate the development of a self-administered test for ovulation detection since relatively simple colorimetric assays are available and may be used in a kit for domicilary use.

Billings and co-workers[19] reported that women attending the Family Planning Center in Melbourne, Australia, were able to predict and identify the time of ovulation by recognizing a pattern of vaginal mucus discharge which occurs about the time of ovulation. In 22 subjects, the authors measured plasma LH and urinary total estrogens and pregnanediol daily in the midcycle to provide a hormonal estimate of the day of ovulation. A characteristic lubricative mucus identified by all the women occurred on the day of ovulation in five, on one day before ovulation in nine, and two days before ovulation in four. The mean onset of perceptible mucorrhea occurred 6.2 days before ovulation. Billings and associates[19] concluded that the time of ovulation can be identified clinically by recognizing increased midcycle mucus discharge.

Combined with the perception of mucorrhea, self-detection of cervical mucus alkaline phosphatase may provide an accurate method of *ovulation prediction* so urgently needed both in infertility investigations and for the development of a reliable method of natural family planning. Studies are currently in progress to determine the feasibility of such an approach.

The authors wish to express their gratitude to John Gorham, Ph.D., for his assistance in statistical analysis.

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Review Course in Obstetrics and Gynecology

Columbia University College of Physicians & Surgeons announces its annual postgraduate course entitled, "Review Course in Obstetrics and Gynecology," to be held at Columbia-Presbyterian Medical Center, Monday through Friday, October 25-29, 1976. Some of the speakers are Drs. R. Vande Wiele, R. Richart, R. Neuwirth, associates, and guest lecturers. It will include a survey of the major clinical and pathologic problems pertaining to the female reproductive system. Emphasis will be on the diagnosis and management of obstetric and gynecologic disorders, including infertility, endocrine problems, and malignant diseases, with the use of modern advances in basic knowledge and clinical practice. There will be a review of gynecologic pathology. The course is divided as follows: gynecologic oncology, perinatal medicine, gynecology and obstetrics, reproduction control behavior, and endocrine disorders. The fee is $250 (residents $125). For registration, write to: Jose M. Ferrer, Jr., M.D., Associate Dean, 630 W. 168th St. New York, New York 10032. Telephone: (212) 694-3682.

Action of a midcycle contraceptive (R 2323) on the human endometrium

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Over 2,148 cycles of midcycle oral administration of R 2323 (50 mg. per day on Days 15, 16, and 17), the authors recorded a drug-failure pregnancy rate of 5 per cent and an unusually regular cycle length of 28 ± 2 days. During this trial, endometrial biopsies obtained in the luteal phase were examined by light and electron microscopy and compared to pretreatment biopsies. Light microscopy indicated a weakly secretory endometrium suggestive of some, albeit low, progesterone impregnation. Ultrastructural examination revealed deleterious changes in the development of the nucleolar channel system and giant mitochondria and a delay in the migration of glycogen granules. This low progesterone impregnation could be explained either by a direct effect of R 2323 on cell ultrastructure or by interference with progesterone availability. It would appear that R 2323 acts as a temporary substitute for progesterone at the receptor level but that it does not induce all the biological manifestations of this hormone, in particular, the endometrial changes required for implantation.

LABORATORY investigation of the activity of the steroid R 2323 (13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,9,11-trien-20-yn-3-one) suggested that this compound might be a suitable candidate for a novel approach to contraception. In animal studies, R 2323 exhibits marked antiprogesterone activity which is independent of its moderate antiestrogenic activity but probably related to its weak progestomimetic activity[1]; in biochemical studies, it competes for the uterine cytosol progesterone, but not estradiol, receptor.[2, 3] These observations were the basis of the hypothesis that flooding of progesterone binding sites at the beginning of the luteal phase with postovulatory administered R 2323 might prevent progesterone-induced changes and consequently implantation. Indeed, over the first 1,300 cycles of a clinical trial involving oral administration of 50 mg. of R 2323 per day on Days 15, 16, and 17 of the cycle, a relatively low pregnancy rate was recorded.[4] This contraceptive efficacy was maintained until the close of the trial. The final results are presented in this paper.

During the early secretory phase, the human glandular epithelium is characterized by the presence of a functional triad consisting of glycogen granules and giant mitochondria, which begin to develop late in the proliferative phase, and nucleolar channels, which only appear after ovulation at the onset of progesterone secretion. The development of these structures has, to some extent, been correlated with progesterone impregnation. In the course of the above clinical trial, the impact of postovulatory administered R 2323 on this development was examined at cellular and subcellular levels by light and electron microscopy. The results of this study are reported in the present paper.

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Material and methods

Clinical administration schedule. The study was performed in 160 healthy fertile women with regular menstrual cycles at the Maternity Clinic, Port-au-Prince, Haiti. They received by the oral route, once

Table I. Number of biopsies examined

Day	Pretreatment	Treatment cycle 1	2	3	4	5	6	7	8
18 or 19	28	24	5		10	8	2		1
25 or 26	8		3	4	3	3			

Table II. Percentage of cycles which meet the classic criteria of cycle length and bleeding

Months of exposure	No. of cycles	Percentage of cycles: Cycle length 24-32 days	Bleeding 3-5 days	Without spotting
1-3	468	83	83	97
4-6	423	84	82	96
7-9	350	85	88	99
10-12	276	85	87	96
13-24	560	86	87	99
25-36	65	100	91	100
37-40	6	100	100	100

Table III. Pregnancy rate

Months of exposure	No. of cycles	Pregnancies: Drug failure	Patient failure	Total
1-3	468	1	1	2
4-6	423	1		1
7-9	350	3	2	5
10-12	276	1	2	3
13-24	560	3	3	6
25-36	65			
37-40	6			
Total	2,148	9	8	17
Pregnancy rate per 100 woman years		5%	4.5%	9.5%

daily for three consecutive days, capsules containing 50 mg. of R 2323 (13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,9-11-trien-20-yn-3-one); these were administered exactly two weeks following the onset of menses (Days 15, 16, and 17 of the cycle). The following parameters were studied: length of cycle, duration of menstrual bleeding, spotting, contraceptive efficacy evaluated in terms of use-effectiveness by the "Pearl Index" (failure rate per one hundred woman years or 1,200 cycles per year), and omissions.

Endometrial biopsies from 36 women chosen at random at admission were taken with a Novak curet either in the early secretory phase (Day 18 or 19) or in the late secretory phase at the presumed implantation time (Day 25 or 26) and compared to "pretreatment biopsies" from the same women taken at similar times immediately prior to treatment. At least two biopsies were taken from each woman over eight treatment cycles (Table I).

Histologic techniques. For light microscopy, endometrial biopsies were fixed in Bouin alcoholic fluid and embedded in paraffin wax. Sections 5 μ thick were stained with hematoxylin and eosin, Masson's trichrome stain, and periodic-acid–Schiff (PAS) reagent and examined according to the criteria of Noyes and associates.[5] For electron microscopy, biopsies were immediately fixed by immersion in 4 per cent glutaraldehyde (buffered to pH 7.3 in 0.1M phosphate buffer at 4° C.), rinsed in buffer, cut in small fragments, and postfixed for one hour in phosphate-buffered 1 per cent osmium tetroxide (pH 7.4 at 4° C.). Specimens were dehydrated through a graded series of ethanol and embedded in Epon 812. Blocks were cut with glass or diamond knives on an LKB Ultrotome III. Sections 1 μ thick were mounted on glass slides and stained with 0.5 per cent toluidine blue in 0.5 per cent sodium borate for light microscopic examination. Ultrathin sections were mounted on Formvar-coated grids and stained with uranyl acetate followed by lead citrate for examination with an electron microscope* at 80 kv.

Results

Clinical study. Cycle length was extremely regular throughout treatment (Table II). Approximately 85 per cent of cycles fell within the range of 24 to 32 days. The mean cycle length was 28 ± 2 days.

About 85 per cent of incidences of menstrual bleeding lasted from three to five days. There was virtually no spotting (Table II).

Seventeen pregnancies occurred during the study, giving rise to a general failure rate of 9.5 per 100 woman years (Table III). Nine of these pregnancies were considered as drug failures and eight were considered as patient failures. All eight patients had omitted all three capsules during one cycle.

Histologic study.

Day 18 or 19 biopsies (early secretory phase).

PRETREATMENT BIOPSIES. Endometrium from pretreatment biopsies was early secretory and characterized by the following features when viewed by light microscopy (Fig. 1, *a*): little basal vacuolation of the epithelium, basal location of nuclei, rare mitoses, a highly PAS-sensitive cell apex, and some intraluminal secretion. Small patches of edema were visible in the stroma. In some instances, the endometrium was typical of the stage of preovulatory estrogen im-

*Elmiskop 101, Siemens A.G., Germany.

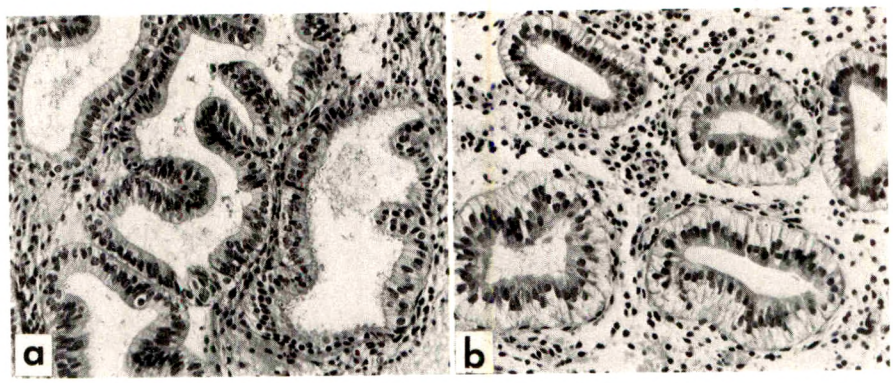


Fig. 1. Photomicrographs of Day 19 endometrial biopsies (paraffin sections). Pretreatment *(a)*: tortuous glands, little basal vacuolation, and intraluminal secretion. Fourth treatment cycle *(b)*: tubular glands, marked basal vacuolation, no intraluminal secretion, and some stromal edema. (Hematoxylin and eosin. Original magnification ×225.)

pregnation or of a transition stage between the late proliferative and secretory phases, suggesting either anovulation or delayed ovulation.

Electron microscopic data confirmed the secretory aspect of the glandular epithelium (Fig. 2, *a* and *b*). The main features were: presence of glycogen granules and numerous microvilli at the cell apex; presence of giant mitochondria, surrounded by semirough endoplasmic reticulum, at the cell base; extensive development of the Golgi apparatus; presence of nucleolar channels in the nuclei. In most cases, these channels were surrounded by a layer of dense granules and were capped by the nucleolus (Fig. 3, *a*). According to Fig. 4, it would appear that direct communication occurs between the channels and the perinuclear space and that the interchannel matrix and cytoplasm are contiguous at the level of the nuclear pores. Very dense glycogen granules were found in the stromal cells.

BIOPSIES OBTAINED DURING TREATMENT. Endometrium from biopsies obtained during treatment was, in all cases, when viewed by light microscopy (Fig. 1, *b*), typical of the midcycle transition stage between the late proliferative and secretory phases. It was characterized by: widespread subnuclear vacuolation of the glandular epithelium as indicated by the presence of PAS-sensitive material at the cell base, dilated glands with regular outlines, rare mitoses, and no or little intraluminal secretion. Stromal edema was slightly more pronounced than at the pretreatment stage. No notable variations were recorded as treatment progressed.

Examination of the fine structure by electron microscopy (Fig. 2, *c* and *d*) revealed few microvilli at the cell apex and massive accumulation of glycogen granules in the subnuclear region throughout treatment. The mitochondria were mostly small, elongated, and clustered at the base of the cell during the first two treatment cycles. The endoplasmic reticulum was dispersed throughout the cytoplasm and not well developed. Giant mitochondria were rare but reappeared surrounded by the endoplasmic reticulum as of the fourth treatment cycle. The Golgi apparatus was less well developed than at the pretreatment stage. Nucleolar channels were either missing or rudimentary during the first two treatment cycles. They appeared distorted and dilated, even totally broken down. The dense granules encircling the system were also missing and were replaced by a clear zone forming a kind of halo (Fig. 3, *b* and *c*). From the fourth treatment cycle onward, however, an ordered channel system reappeared, but this was less extensive than at the pretreatment stage and in most instances was not surrounded by dense granules or capped by the nucleolus (Fig. 3, *d*).

Day 25 or 26 biopsies (late secretory phase).

PRETREATMENT BIOPSIES. Endometrium from pretreatment biopsies, when viewed by light microscopy, was either typical of a late secretory phase with characteristic dilated, tortuous glands or showed weak secretory activity.

Electron microscopic studies revealed in most cells the disappearance of nucleolar channels and of giant mitochondria, glycogen granules dispersed throughout the cytoplasm, nuclei with irregular contours and numerous invaginations, a highly developed supranuclear Golgi apparatus, microfilament bands crossing the cell, and a highly folded cytoplasmic membrane. The presence in some cells of large autocytolysosomes was a sign of increased lysosomal activity and cell degeneration. Numerous microvilli formed spikes into the lumen. Some intraluminal secretion was still visible. The stromal cells were round and had a highly

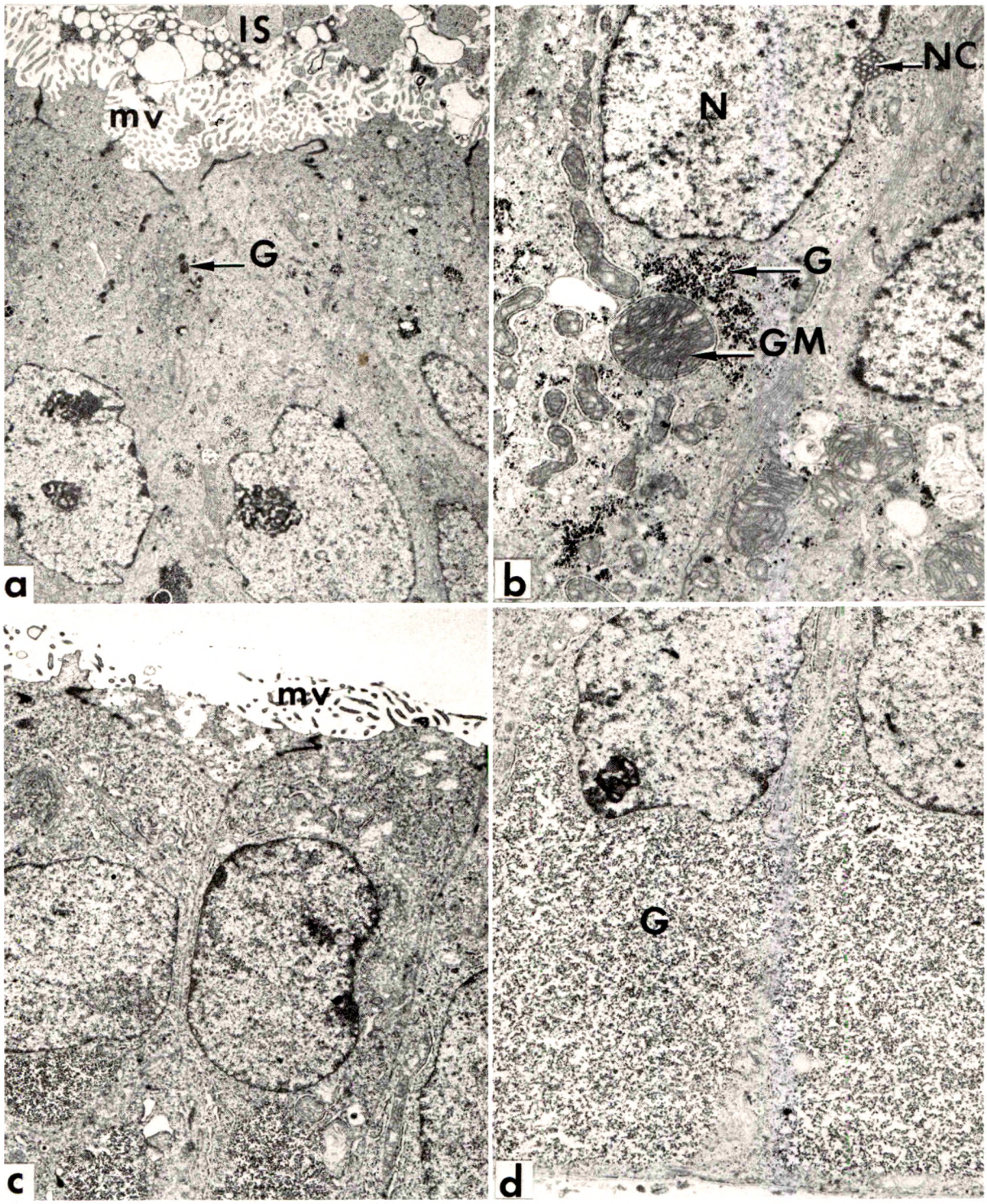


Fig. 2. Electron micrographs of glandular epithelium from Day 19 endometrial biopsies. Pretreatment: *a*, cell apex with small clusters of glycogen granules *(G)*, numerous microvilli *(mv)*, and intraluminal secretions *(IS)* (×4,600); *b*, cell base with small patches of glycogen granules, giant mitochondria *(GM)*, and a nucleolar channel system *(NC)* in the nucleus *(N)* (×9,400). Fourth treatment cycle: *c*, cell apex with few microvilli *(mv)* and no intraluminal secretions (×5,500); *d*, cell base with massive accumulation of glycogen granules *(G)*, no giant mitochondria, and no nucleolar channel system (×7,500).

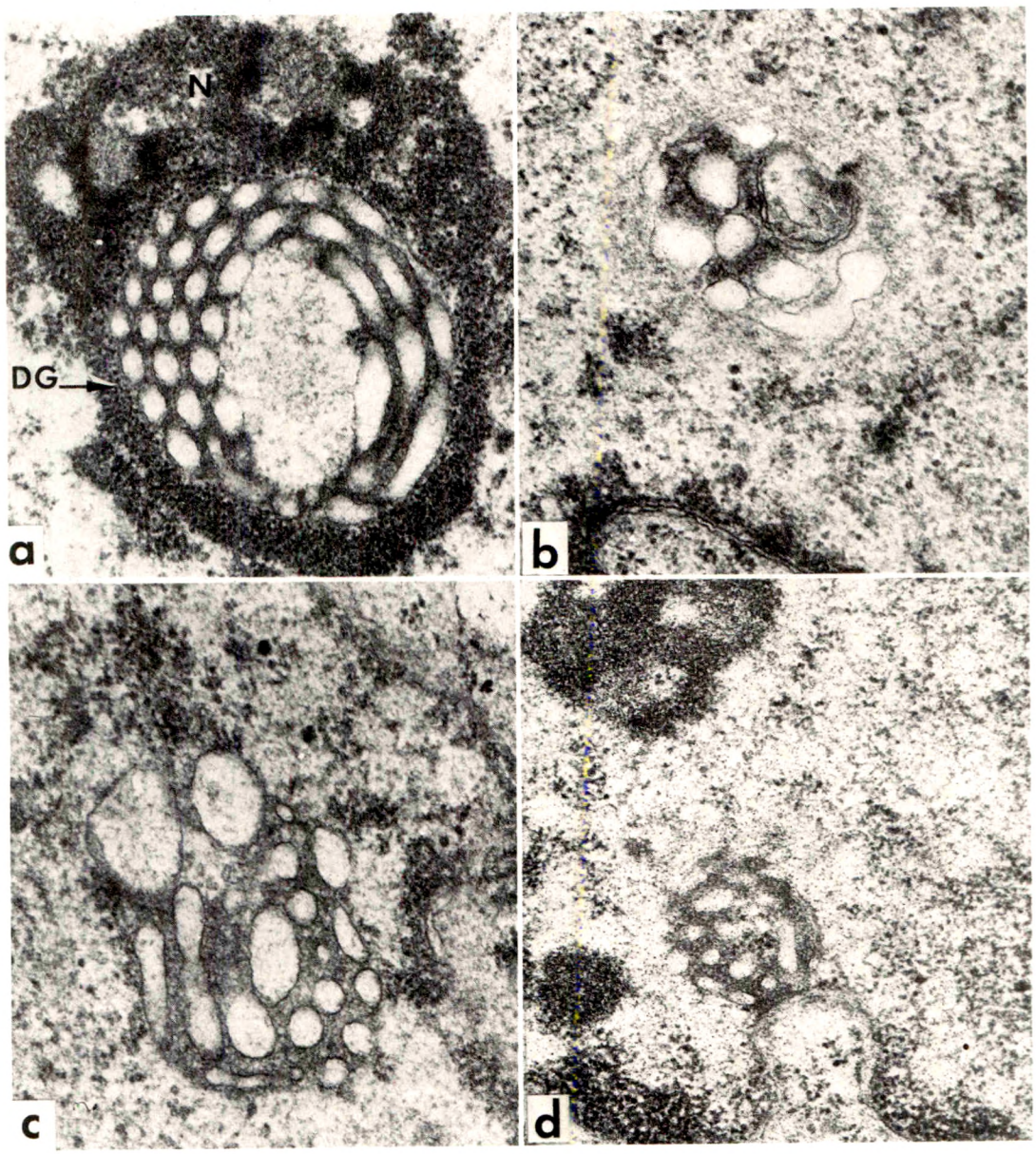


Fig. 3. Electron micrographs of nucleolar channel system from Day 19 endometrial biopsies. Pretreatment *(a)*: highly ordered channel structure capped by the nucleolus *(N)* and encircled by dense granules *(DG)*. First treatment cycle *(b* and *c)*: there is random deleterious changes of the channel system; the channels are distorted, sometimes dilated, and even totally broken down. The dense granules are missing, and the nucleolus is not in the vicinity of the channel system. Fourth treatment cycle *(d)*: ordered channel system but less well developed than at the pretreatment stage. The dense granules are still missing, and the nucleolus is at a distance. (×50,000.)

developed Golgi apparatus and granular endoplasmic reticulum. An extensive network of collagen fibers also was visible. In some instances, these cells infiltrated the epithelial layer.

BIOPSIES OBTAINED DURING TREATMENT. Endometrium from biopsies obtained during treatment, when viewed by light microscopy, differed only slightly from pretreatment endometrium. Instances of low intraluminal glandular secretion were noted, in particular, toward the fourth and fifth treatment cycles, indicating a decrease in secretory activity as treatment progressed.

Electron microscopic studies also revealed slight divergences from pretreatment endometrium. In general, a reduction in glandular epithelial height was observed. The glandular cells showed signs of decreasing secretory activity accompanied by regression of the



Fig. 4. High-power electron micrograph of nucleolar channel system from Day 19 pretreatment endometrial biopsy showing two interesting features: communication between the channels *(C)* and the perinuclear space *(PS)* at Point *a* and contact between the interchannel matrix and the cytoplasm via two nuclear pores at Points *b* and *b′*. *N* = Nucleolus; *DG* = dense granules. (×135,000.)

Golgi apparatus and the ribosomes. The nuclei were clear, elongated or round, with regular outlines, and located at the base of the cell.

Comment

In a clinical trial involving midcycle administration of R 2323, a pregnancy rate (Pearl Index) of only 5 per cent (drug failure) was recorded. The treatment did not upset the normal menstrual cycle or the onset of the following cycle; cycle length and bleeding were unusually regular, and no spotting occurred. No side effects were associated with the treatment.

Two major observations could be drawn from a preliminary viewing of the endometrium by light microscopy. First, biopsies obtained during midcycle R 2323 treatment late in the secretory phase (Day 25 or 26 biopsies) differed little from pretreatment biopsies. They showed distinct signs of some, albeit low, secretory activity, indicating that, even during treatment, some progesterone impregnation occurs. However, because of the epithelial degeneration associated with the approach of menses, they were unsuitable for the assessment of R 2323 activity. Second, biopsies obtained early in the secretory phase (Day 18 or 19 biopsies) were rather heterogeneous in aspect prior to treatment but exhibited a spectacular similarity in likeness during treatment. During treatment, the aspect of the endometrium suggested luteal insufficiency.

This interpretation of the appearance of human endometrium from Day 18 or 19 biopsies obtained during treatment was confirmed by electron microscopic studies which laid particular emphasis on the development of the nucleolar channel system and of the giant mitochondria and on the assessment of the secretory activity of the endometrium as determined by the amount and location of glycogen granules. R 2323

induced morphologic changes in the channel system and mitochondria and interfered with endometrial secretion.

In a normal cycle, the nucleolar channel system appears shortly after ovulation (Days 15 and 16), its appearance being closely linked with the presence of progesterone.[6] Its function is, as yet, unelucidated, but certain observations imply a role in the transfer of material between chromatin, which contains the genetic information, and the cytoplasm where protein synthesis occurs. The nucleolus migrates toward the membrane; on about Day 18, the channels are seen to be capped by the nucleolus, and direct contact is established between the channels and perinuclear space as well as between the interchannel matrix and cytoplasm via nuclear pores. The nucleolus then drifts away from the channel system, leaving it in contact with the membrane.* Toward the end of the cycle, the channel system breaks down and protrudes into the cytoplasm prior to complete lysis in the giant lysosomes.[7] The migration of the nucleolus toward the membrane and the establishment of contact imply that it has a role in the transfer of information. Moreover, a channel system is a morphologically ideal structure for rapid communication with the possibility of a high level of passage into or out of the channels because of a large surface area. More and colleagues[7] have, in fact, suggested that this system might be involved in the rapid transfer of new messenger ribonucleic acid to the cytoplasm.

During midcycle R 2323 treatment, the channel system is missing or rudimentary during the first two treatment cycles, whether in Day 18 or 19 biopsies as reported here or in Day 22 or 23 biopsies as observed in a preliminary study.[8] However, it reappears from the fourth treatment cycle but in a form which is less well developed than the normal structure. It is no longer surrounded by dense granules and is not surmounted by the nucleolus which remains at a distance. These observations suggest that the channel system is unable to act as a liaison between the nucleolus and perinuclear space because of faulty development or an ill-synchronized link-up.

In a normal cycle, the giant mitochondria of glandular cells attain peak development[9] on Days 19 and 20, when progesterone secretion has not quite reached a maximum, the increase in volume and crest surface being, in all likelihood, due to intensified oxidative phosphorylation reactions.[10, 11] During the first couple of cycles of R 2323 treatment, no or few giant mitochondria were visible, suggesting either incomplete or delayed endometrial development. According to the hypothesis that mitochondrial size might be influenced by progesterone,[12] this incomplete development would reflect progesterone insufficiency. The reasons for the subsequent reappearance of giant mitochondria from the fourth treatment cycle remain unclear.

Glycoproteins are the main secretory product of the endometrium and are probably derived from the glycogen granules in the epithelial cells. At the beginning of the secretory phase of a normal cycle, these granules accumulate rapidly and in a great number at the base of the cells; three to four days after ovulation, they are detected at the cell apex. Throughout midcycle R 2323 treatment, the glycogen granules were still at the cell base on Day 18 or 19, indicating that their degradation by ergastoplasmic enzymes was being delayed and that they were not being used for the synthesis of glycoproteins. The resultant deficiency in glycoprotein secretion points to progesterone insufficiency.

This progesterone insufficiency, also reflected in the impaired development of the nucleolar channel system and giant mitochondria, could be correlated with the drop in plasma progesterone determined radioimmunologically after midcycle R 2323 administration.* However, this observation alone cannot account for its action since other compounds which have the same effect on plasma progesterone levels do not give rise to the same histologic and clinical manifestations. The estrogen diethylstilbestrol (DES), which has been successfully used in clinical trials as an antiimplantation agent, decreases plasma progesterone and, moreover, modifies nucleolar structure but, unlike R 2323, upsets the bleeding pattern, sometimes even to the extent of affecting subsequent cycles.[13, 14] With R 2323, bleeding is unusually regular. The progestin norethindrone decreases plasma progesterone but maintains, and does not impair, the development of the nucleolar channel system and giant mitochondria.[15] Attempts to use it as a postovulatory contraceptive have ended in failure because of an unacceptable pregnancy rate and irregular bleeding.[16] The differing actions of R 2323 and norethindrone on the nucleolar channel system and implantation seem to confirm the observations by Gore and Gordon[17] on unexplained sterility which imply that the nucleolar channel system might be involved in implantation.

The mechanism of R 2323 interference with the

*Unpublished observations.

*To be published.

progesterone action remains unknown. Midcycle treatment has little effect on luteinizing hormone secretion* and, unlike DES and progestins, such as norgestrel and chlormadinone acetate, R 2323 does not inhibit ovarian progesterone biosynthesis. Histochemical studies in the guinea pig have revealed no change in Δ5-3β-*ol*-dihydrogenase activity. However, R 2323 might exert a direct action on the endometrium, as has been demonstrated in vitro for DES.[13]

A partial interpretation of the results may be offered in terms of existing biochemical data. R 2323 competes with progesterone for uterine cytosol progesterone-binding sites.[2, 3] These sites are induced by estradiol, which, although secreted virtually throughout the cycle, attains a maximum level of secretion during the proliferative phase. Therefore, the concentration of these sites is very high immediately after ovulation, at a time when the progesterone level is still low. Consequently, just after ovulation, the majority of these sites are unoccupied or potentially "occupiable" by postovulatory administered R 2323. Thus, temporary substitution of progesterone by R 2323 at the receptor level might prevent the induction of the biological responses of the natural hormone. These annulled responses cannot be compensated by a "mimetic" progesterone-like activity since R 2323 is only a weak progestin and, moreover, does not maintain pregnancy in the castrated animal.[1] Furthermore, the action of R 2323 would be reinforced by its antiestrogenic activity which might hinder any further synthesis of estradiol-produced progesterone receptor sites. The temporary desynchronization of early events in the luteal phase, caused by substitution of progesterone by R 2323, is probably such that the conditions required for implantation are rarely fulfilled (Pearl Index = 5 per cent). However, the imbalance is not marked enough to upset the normal menstrual cycle or the onset of the following cycle. In this, R 2323 differs from compounds such as diethylstilbestrol, norethindrone, and oxymetholone which have turned out to be clinically unacceptable.[14, 16, 18]

*To be published.

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Course in Gynecologic Laparoscopy

A course in "Gynecologic Laparoscopy," sponsored by the New Jersey Fertility Foundation, will be held October 14 and 15, 1976, in Roselle Park, New Jersey. For further information, contact: S. A. Wilchins, M.D., 14 E. Westfield Ave., Roselle Park, New Jersey 07204.

Progestational agents and blood coagulation

VII. Thromboembolic and other complications of oral contraceptive therapy in relationship to pretreatment levels of blood coagulation factors: Summary report of a ten-year study

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During a ten-year period, 348 women were studied for a total of 5,877 patient months in four separate studies relating oral contraceptives to changes in hematologic parameters. Significant increases in certain factors of the blood coagulation and fibrinolysin systems (factors I, II, VII, VIII, IX, and X and plasminogen) were observed in the treated groups. Severe complications developed in four patients. All four had an abnormal blood coagulation profile, suggesting "hypercoagulability" before initiation of therapy. Some of these findings represented the most extreme abnormalities seen in the entire group of patients; some increased further during therapy. One of these patients developed a myocardial infarction before receiving any medication, shortly after the base-line values were obtained. One patient developed retinopathy 19 months after she began therapy, and another developed thrombophlebitis after 27 months of therapy. The fourth patient developed thrombophlebitis 14 days after initiation of contraceptive therapy. All four patients were of the A or AB blood group. Previous studies suggested the possibility of increased propensity for thromboembolic episodes in patients possessing the A antigen. It appears from these data that hematologic work-ups may be useful in women who are about to start long-term oral contraceptive therapy.

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IN A SERIES of previous studies,[1–7] our group investigated the effects of various oral contraceptive regimens on the blood coagulation and fibrinolysin systems. We found,[8] as did other investigators, that oral contraceptives increase circulating blood levels of several procoagulants and fibrinolytic system components and that these effects are related primarily to the estrogen portion of the oral contraceptives. However, despite significant rises in levels of certain blood coagulation parameters, we observed only one instance of thromboembolism during our studies.[4] The question then arose as to the relationship of the assays we performed to clinical hypercoagulability and actual thrombosis. We postulated that the observed increases in coagulation factors with concomitant increases in fibrinolytic factors might maintain a hemostatic balance, thereby avoiding evident thromboembolic

phenomena. But, upon retrospective review of all our data, we found that there were indeed three other instances of serious side effects in women who were about to enter our studies but were withdrawn, who completed these studies and continued with the same medication, or in whom the complications were not clearly thromboembolic in nature. Most interestingly, however, each woman, including the one we had reported, demonstrated some remarkably abnormal finding(s) in the pretreatment blood sample as well as in subsequent sampling. Since blood samples were collected and stored for various lengths of time before being analyzed (in order to test groups of samples simultaneously), the significance of some of these laboratory findings went unrecognized until the particular study had been completed and statistically analyzed. This was usually long after the occurrence of the clinical episode.

It would be of great value to establish a spectrum of laboratory tests which could be used to evaluate possible predisposition to thrombosis of a patient who is to be given oral contraceptive medication and thereafter to monitor, at regular intervals, the effects of this medication. Perhaps this report may help to validate this concept and suggest a few hematologic parameters that should be measured before and during hormonal contraceptive therapy. Despite the extensive literature on blood coagulation changes in women receiving various types of oral contraceptives and on the epidemiology of thromboembolism,[8] no clinical correlation was established or even studied between changes in the blood coagulation and fibrinolysin systems and clinical complications.

Subjects, material, and methods

The effects of oral contraceptive medications upon the blood coagulation and fibrinolysin parameters of women were investigated during four separate clinical trials, over a ten-year period.[1–4] In Trials 1, 2, and 3, decreasing dosages of a synthetic progestational agent (norethindrone acetate) were used in combination with a standard amount of a synthetic estrogen (ethinyl estradiol),* and in Trial 4 a progestin† alone was compared with a norethindrone-mestranol conbination.‡

Table I lists the medications and dosages that were given to each group in each trial. A total of 348 women (262 treated, 86 control) were entered into the studies, but many dropped out before completion of projected trial times. However, we were able to accumulate data reflecting 5,877 combined treated-control patient observation months.

All of the women were healthy volunteers* of child-bearing age. Preprandial blood samples were drawn from them before they started treatment and at defined intervals throughout each trial period. Blood was obtained from control patients at similar intervals. Some laboratory studies were performed immediately after the blood samples were collected, but the majority of determinations were carried out in the laboratory after the plasma had been separated and stored in freezers. We employed a wide spectrum of methods in an attempt to obtain a complete survey of the status of each woman's coagulation-fibrinolysin mechanism, at each period of blood sampling. The tests included general screening assays as well as specific measurements of individual factors and components, all designed to quantitate procoagulant levels and activity relationships of these procoagulants when combined. The assays could demonstrate both decreases in factor levels (hypocoagulability indicators) and increases (interpreted as indication of the so-called "hypercoagulable state"). References to the details of these methods have been given in each of the previously published reports.[1–4] Not all of the assays were performed in each clinical trial. Some were added to and some were eliminated from individual trials during the ten-year study, depending upon the test's applicability or presumed necessity. Those which are an integral part of this report were platelet count,[9] thrombelastography,[10] thromboplastin generation time screening test[11] with calculation of "Generation Factor units (G. F. units),"[1] prothrombin,[12] factor VII,[13] factor VIII,[14] factor X,[15] fibrinogen,[16] plasminogen,[17] and total antiplasmins.[17]

During the course of each trial, observed clinical side effects were recorded for each patient, and laboratory information was accumulated as tests were performed. However, it was not until the individual trials were completed that treatment codes were broken and data were carefully analyzed. These periods (from the beginning of the study to the completion of statistical analysis) ranged from one to four years, sometimes overlapping other trial periods. The laboratory teams were unsure of the relationship of individual patient laboratory measurements to serious side effects, if they occurred. It was not until all four of the trials had been

*Norlestrin, 2, 5, and 1 mg. and sequential, Parke, Davis & Co., P.O. Box 118 GPO, Joseph Campau Ave. At the River, Detroit, Michigan 48232.

†Normenon.

‡Norinyl, Syntex Laboratories, Inc., Stanford Industrial Park, Palo Alto, California 94304.

*Informed consent was obtained from each woman after the nature of the study had been fully explained to her.

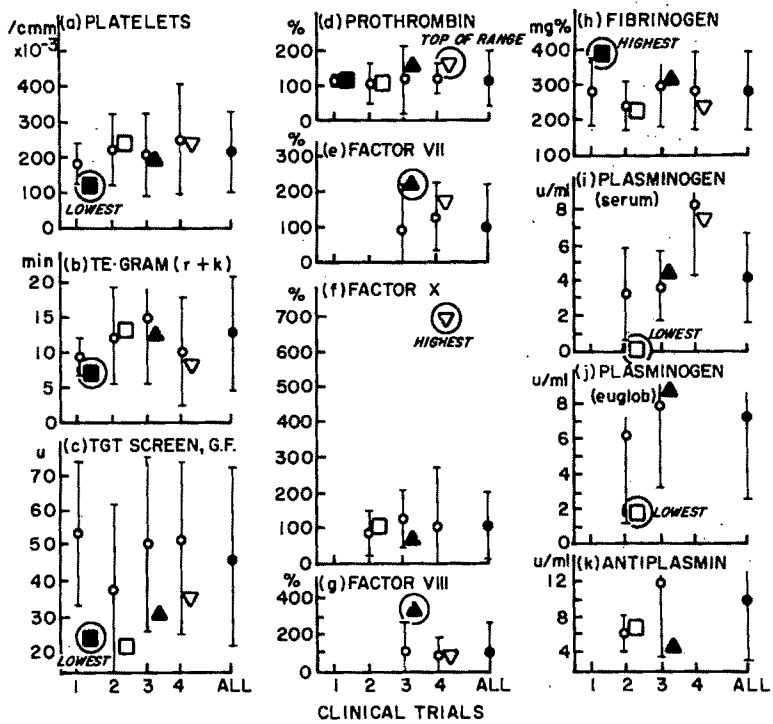


Fig. 1. Oral contraceptive medication clinical trials—pretreatment levels of selected parameters (means ± 2 S.D.) for each group (affected patients' values *not included* in calculations/means). The clinical trial key is given below.

Trial No.	*Progestin*	*Estrogen*	*Affected patients*
1	2.5 mg.	50 μg	Coronary occlusion before treatment started (■)
2	1.0 mg.	50 μg	Retinopathy after 19 months of treatment (□)
3	1.0 mg.*	50 μg*	Thrombophlebitis after 27 months of treatment (▲)
4	1.0 mg.	50 μg	Thrombophlebitis after 2 weeks of treatment (▽)

All = composite values

*Sequential.

completed that we indeed were able to correlate strikingly abnormal pretreatment findings with clinically observed abnormal phenomena in four patients.

Results

Fig. 1 shows the mean pretreatment values (± two standard deviations) for each parameter in each clinical trial and a composite mean for each category. These are values obtained from each group (Table I), with the exclusion of each patient who developed a serious complication during each of the trials. The individual base-line values are indicated by symbols next to the group's mean and standard deviation range.

During Trial 1,[1] ". . . no thromboembolic phenomenon occurred in any of the patients in this study during a 15 to 24 month observation period." However, one woman (E. M., a clinic nurse) who was going to start therapy had a pretreatment blood sample taken but developed anginal chest pains a few days later and was withdrawn from the study before starting medication. One week later, she suffered an anterior myocardial infarction. This 51-year-old woman with the AB blood group was to begin the hormonal regimen to relieve menopausal symptoms (headache, depression, hot flashes, fatigue). When this trial's data were analyzed two years later, it was seen that some of this patient's base-line values, as compared to those of the group, were remarkably out of line and indicative of the "hypercoagulable state." The platelet count was lower than any of the others, suggesting a possible defibrination process (Fig. 1, *a*); the thrombelastogram showed a short clotting time *(b);* the thromboplastin generation time screening test *(c)* was far more rapid than that of anyone else (low G.F. units = rapid clotting), and the fibrinogen level *(h)* was the highest in the group.

Table I

Clinical trial and reference	Treatment	No. of patients		No. of patient months	
		Control	Treated	Control	Treated
Margulis and associates,[1] 1965	2.5 mg. norethindrone acetate + 50 μg ethinyl estradiol (1 tablet daily—Days 5-25 of menstrual cycle)	0	59	0	1,405
Ambrus and colleagues,[2] 1969	1.0 mg. norethindrone acetate + 50 μg ethinyl estradiol (1 tablet daily—Days 5-25 of menstrual cycle)	24	66	450	1,287
Mink and co-workers[3] 1974	1.0 mg. norethindrone acetate + 50 μg ethinyl estradiol (sequential: 1 tablet ethinyl estradiol, Days 5-25; in addition, 1 tablet norethindrone acetate, Days 15-25)	52	112	1,008	1,580
Mink and associates,[4] 1972	1.0 mg. norethindrone + 50 μg mestranol (1 tablet daily for 21 days followed by 1 placebo tablet daily for 7 days)	10*	12	46†	55
	0.5 mg. Chlormadinone acetate (1 tablet daily)	10*	13	46†	46
Totals		86	262	1,504	4,373

*Same patients.
†Same patients.

After Trial 2, we reported, " . . . no clinical sign of hemorrhage or thrombosis has occurred during the 2 year observation period in any of the patients."[2] However, one patient did have another type of serious side effect along with a markedly abnormal laboratory finding. J. D., age 24, blood group AB, developed in the right eye a central, serous, scotoma retinopathy 19 months after beginning oral contraceptive therapy. She had no history of diabetes but was myopic with vision correctable to 20-20 with contact lenses. After the appearance of retinopathy, the vision in her right eye was reduced to 20-60, with no explanation for the etiology of the disorder. The pretreatment laboratory findings were unremarkable except for plasminogen levels (Fig. 1, *i* and *j*), which were lower than those of anyone else in the group. The nine-month blood sample showed a very small rise in the plasminogen level as compared with highly significant rises in the rest of the treated women.

When the third trial was completed, we reported,[3] "During the two-year study period, none of the patients in either group demonstrated any clinical evidence of thrombosis." We subsequently discovered that one patient, J. J., developed thrombophlebitis three months after we had taken the twenty-fourth treatment-month (final) blood sample. She was 34 years old with blood group A and had continued the oral contraceptive medication beyond the two-year trial period. Pretreatment levels of three of the clotting factors were indicative of a "hypercoagulable" condition; thromboplastin generation time screen G.F. units were low (Fig. 1, *c*), and factor VII and VIII levels (*e* and *g*) were at the highest of the group ranges. In subsequent samplings (three, nine, and 24 months), these parameters, as well as the others studied, exhibited significant rises.[3]

During the fourth trial,[4] D. B. (age 25, blood group A) started progestin-estrogen treatment six weeks post partum. After 14 days of medication, she developed deep-vein thrombophlebitis in the left calf, at which time the treatment was discontinued. The base-line blood sample parameters compared with the assays of entire group showed a prothrombin level (Fig. 1, *d*) at the top of the range and a factor X level (*f*) of *700 per cent*, far out of the ordinary range.

Comment

In our studies with 348 women (those receiving oral contraceptives or control subjects), we monitored the changes which occurred in hematologic parameters over a total of 5,877 patient months. We considered significant increases from pretreatment levels of procoagulants to be indicative of induced hypercoagulability. Despite major changes observed in certain clotting parameters (e.g., prothrombin, factor VII, factor X), we observed no thromboembolic complications during the study except in one patient (D. B., in Trial 4). An ophthalmologic complication, not necessarily thromboembolic in nature, was seen in another patient (J. D., in Trial 2). We interpreted these clinical findings as evidence of a continual maintenance of the dynamic hemostatic balance due to a compensatory increase in

the levels of fibrinolytic factors (plasminogen). Upon retrospective analysis, we found that two additional patients developed thromboembolic complications, one who was scheduled to enter the study but never did (E. M., Trial 1), the other after completing the two-year study while continuing the same treatment (J. J., Trial 3). All four patients with serious complications had high pretreatment levels of several hematologic parameters. It appears that pretreatment levels of certain blood coagulation components were extraordinarily high and subsequent increases occurred during treatment, thus upsetting the dynamic hemostatic balance and producing overt thrombotic sequelae. Obviously there is a large gap between the existence of laboratory evidence of in vitro "hypercoagulability" and the occurrence of clinical thromboembolism. The latter may be dependent not only upon the alteration of the various factors involved in blood coagulation but also on changes in blood viscosity, velocity of blood flow, and the status of the blood vessels themselves.

Recently, evidence has been presented[18] which suggests that the absence of normal levels of vessel wall fibrinolysin activators may predispose to thrombosis; women with this (or another) pre-existing abnormality might develop thrombotic complications whether or not they used oral contraceptive medications. The affected patients in our trials might have been in a similar "predisposed" category.

Patient E. M. (Trial 1), who developed coronary occlusion before oral contraceptive therapy was instituted, demonstrated a paradoxical combination of rapid clotting times in two screening assays and a low platelet count, all suggestive of a certain degree of intravascular clotting ("consumption coagulopathy"), together with a puzzlingly high fibrinogen level. It had long been considered axiomatic that "consumption coagulopathy" also was characterized by a low fibrinogen level, reflecting the "clotting out" of this protein. However, we have found the opposite to be true in certain cases.[19] There may be a reactive hyperfibrinogenemia (three to four times normal levels) in response to increased catabolism of fibrinogen.

Although Patient J. D. (Trial 2) exhibited no abnormally high levels of clotting factors, the low pretreatment plasminogen might have been indicative of a potential imbalance in the dynamic hemostatic mechanism. We have no evidence that the retinopathy was thrombotic in origin, but it is possible that the increases in procoagulants induced by the oral contraceptives might have tipped the scale toward a clotting episode.

Little is known about the ophthalmic side effects of contraceptive steroids or their components. There have been a few reports of patients receiving sex hormones or combined ovulation inhibitors who developed pseudotumor cerebri with occlusion of papilli,[20] thrombosis, migraine, apoplexy, optic nerve edema, and transient reduction of the visual field.[21, 22] This paucity of information may, in part, relate to the lack of detailed, serial ophthalmologic work-ups in many clinical protocols aimed at the study of oral contraceptives.

Patient J. J. (Trial 3), who demonstrated abnormally high pretreatment levels of procoagulants, did not develop thrombophlebitis until after two years of therapy. Perhaps there is a point at which the clotting factor levels become critical and thrombosis occurs in response to additional factors. Patient D. B. (Trial 4) already had apparently abnormally high levels of factor X and prothrombin (two immediate precursors of thrombin formation) before she started hormonal therapy. Within two weeks of initiation of treatment (with possible additional increases in these clotting factors), a thromboembolic episode occurred.

A further comparison of the four women showed that they all shared blood group antigen A (E. M., AB; J. D., AB; J. J., A; D. B., A). This was especially interesting since we previously found[6] an indication of hypercoagulability in group A women as compared to group O individuals, as evidenced by lower thromboplastin generation time G.F. units. Studies by other investigators on the relationship between blood groups and blood coagulation were also reviewed in this paper. All data suggest increased propensity for "hypercoagulability" related to blood group antigen A.

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Effect of oral contraceptives on nutrients

III. Vitamins B_6, B_{12}, and folic acid

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The interactions of oral contraceptive agents (OCA's) with vitamins were studied in a large population of women. In the upper socioeconomic groups, higher incidences of abnormal clinical signs related to vitamin deficiencies were seen in OCA users than in the control subjects. Plasma pyridoxal phosphate and red cell and serum folate were lower in subjects using OCA's in the upper socioeconomic group as compared to levels in the control subjects. Reduction in erythrocyte glutamic oxalacetic transaminase (EGOT) activity and elevation in the EGOT-stimulation test were observed in subjects using OCA's in both upper and lower socioeconomic groups. These observations suggest a relatively deficient state with respect to vitamins B_6 and folic acid in OCA users. No significant effect on serum vitamin B_{12} was observed as a result of OCA administration.

ALTERATIONS in the metabolism of vitamins as a result of the administration of oral contraceptive agents (OCA's) have been reviewed by several authors. Lumeng and associates[1] and Hontz and colleagues[2] observed a significant reduction of plasma pyridoxal phosphate (PLP) levels in OCA users. Our preliminary data[3] suggested that in the high-income groups plasma PLP levels were lower in OCA users as compared to control subjects. However, Brown and co-workers[4] found no differences in plasma PLP levels between oral contraceptive users and nonusers receiving controlled intakes of vitamin B_6.

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Table I. Number of subjects in the clinical and biochemical studies

Group	No. of studies	
	A	*B*
No OCA use	127	103
Pill 1	37	112
Pill 2	44	123
Resumption of pill (RP)	97	105

Wertalik and associates[5] and Davis and Smith[6] observed a reduction in vitamin B_{12} levels in women using OCA's. Reductions in serum folate levels in OCA users have been reported by Shojania and colleagues[7] and Streiff.[8] Streiff also found that naturally occurring folate polyglutamates were poorly absorbed in volunteers using OCA's, although the monoglutamate was utilized normally. On the contrary, McLean and coworkers[9] and Pritchard and associates[10] found no alterations in the serum folate levels in OCA users. Our preliminary data indicated that in the high socioeconomic groups erythrocyte folate levels were lower in OCA users as compared to control subjects.[3]

The objective of this paper is to document further

Table II. Incidence of clinical abnormalities (per cent of abnormalities)

Abnormality	*Socio-economic group*	*No OCA*	*Pill 1*	*Pill 2*	*RP*	*None vs. Pill 1*	*None vs. Pill 2*	*None vs. RP*
Hair								
Dry, brittle	A	15.0	24.3	18.2	5.2	—	—	0.03
	B	33.0	36.3	16.3	30.5	—	0.005	—
Easily pluckable	A	9.4	18.9	13.6	3.1	—	—	—
	B	22.3	36.6	12.2	24.8	0.03	—	—
Lips								
Angular lesions	A	1.6	10.8	15.9	2.1	0.02	0.001	—
	B	14.5	17.9	8.9	23.8	—	—	0.05
Teeth								
Caries 4+	A	7.9	45.9	40.9	7.2	0.001	0.001	—
	B	48.5	54.5	41.5	51.4	—	—	—
Debris or	A	8.7	35.1	31.8	7.2	0.003	0.001	—
calculus	B	48.0	54.5	27.6	44.7	0.03	—	—
Tongue								
Filiform papillary,	A	1.6	0.0	2.3	1.0	—	—	—
atrophy	B	7.8	6.3	5.7	8.6	—	—	—
Fungiform papillary,	A	0	0	2.3	0	—	—	—
hypertrophy	B	1.9	1.8	2.4	4.8	—	—	—
Gums								
Marginal redness	A L*	5.5	35.1	31.8	4.1			
or swelling	D*	0.0	2.7	2.3	1.0	0.001	0.001	—
	B L*	33.0	29.5	27.6	26.7			
	D*	5.8	15.2	8.1	14.3	—	—	—
Swollen red	A L*	2.4	16.2	22.7	3.1			
papillae	D*	0.0	8.1	6.8	1.0	0.001	0.001	—
	B L*	17.8	30.4	22.0	20.0			
	D*	5.8	5.4	8.1	6.7	—	—	—
Bleeding gum	A L*	4.7	18.9	6.8	1.0			
	D*	0.0	2.7	6.8	0.0	0.003	0.01	—
	B L*	10.7	15.2	17.1	8.6			
	D*	4.9	4.5	6.5	4.8	—	—	—
Skin								
Dry, scaling	A	2.4	10.8	9.1	3.1	—	—	—
(xerosis)	B	12.6	19.6	8.1	19.0	—	—	—

*L = Localized; D = diffused.

the effects of OCA's on vitamins B_6 and B_{12} and folate metabolism in a large number of subjects representing different groups which were classified based on the use of different OCA's and the socioeconomic levels of the groups.

Material and methods

In this study, female subjects between the ages of 18 and 45 years were divided into eight groups in a factorial arrangement with two socioeconomic levels and four different hormonal statuses (Table I). The criteria of Myrianthopoulos and French[11] with an income adjustment were utilized in determining the division between the higher (A) and lower (B) socioeconomic classes. Subjects who were not using OCA's belonged to A-none or B-none groups. A-1 and B-1 groups consisted of those subjects who used Norinyl* (1 mg. of norethindrone and 50 μg of mestranol) for 3 months or more. A-2 and B-2 groups of subjects received Ovral* (0.5 mg. of norgestrel and 50 μg of ethinyl estradiol) for three months or more. A-RP and B-RP groups consisted of women who resumed OCA use within five weeks after pregnancy and during lactation.

Subjects in each group were divided further into "supplemented" and "nonsupplemented" subgroups according to whether or not they were using vitamin and/or mineral supplementations, according to their own admission.

PLP was determined by a simple enzymatic assay.[12] Erythrocyte glutamic oxalacetic transaminase (EGOT) was measured in a hemolysate of red blood cells. The cells were washed with 0.85 per cent sodium chloride solution and diluted with saline in a proportion of 0.8

*Syntex Laboratories, Inc., Stanford Industrial Park, Palo Alto, California 94304.

*Wyeth Labs., Div. American Home Products Corp., P. O. Box 8299, Philadelphia, Pennsylvania 19101.

ml. of saline to 1 ml. of packed cells. The test was carried out on 0.1 ml. of a 1:20 hemolysate. For measurement of PLP stimulation, 0.1 ml. of hemolysate was incubated with 0.1 ml. of PLP (0.5 mg. per milliliter) for 20 minutes at 37° C. prior to the colorimetric determination of EGOT.

Erythrocyte and plasma folic acid were determined by a microbiological assay with the use of *Lactobacillus casei*. Serum vitamin B_{12} was measured by a microbiological assay with the use of *Lactobacillus leichmanii*.

Nutritional and biochemical data were analyzed statistically by analysis of variance.[13] Means were ranked by Duncan's new multiple range test.[13] Clinical data were statistically analyzed by the chi-square method.

Results

Dry skin, easily pluckable hair, angular lesions of the mouth, caries and debris of the teeth, marginal redness, swelling, and bleeding of the gums, filiform papillary atrophy, fungiform papillary hypertrophy of the tongue and glossitis, and scaling of the skin were more frequently observed in the B groups than in the A groups. In the A groups some of the above clinical signs were most common in the nonsupplemented groups of subjects. In the A groups, higher incidences of angular lesions of the mouth, caries and debris of the teeth, and marginal redness, swelling, and bleeding of the gums were seen in the OCA users than in the control group (Table II). The incidences of easily pluckable hair, angular lesions of the mouth, and debris or calculus of the teeth were more frequently observed in the B-1 group as compared to the B-none group. A higher incidence of angular lesions of the mouth was seen in the B-RP group as compared to the B-none group.

In general, the intake of vitamin B_6 and folic acid by OCA users did not differ from that in the control subjects. However, the A-RP group of subjects had a higher intake of vitamin B_6 and folic acid than A-1 and A-2 subjects. Although Group A–supplemented subjects had a higher intake of vitamin B_6 and folic acid than the nonsupplemented group, this difference was not very clear in Group B subjects. In general, the intake of vitamin B_6 and folic acid was higher in Group A subjects as compared to that in Group B.

Results of PLP, EGOT, and per cent stimulation of EGOT are presented in Table III. In Group A, the plasma PLP level was decreased due to OCA administration. A supplementation effect was seen mainly in the A groups. Plasma PLP was found to be lower in the A-RP group than in the A-1 and A-2 groups.

EGOT activities were found to be lower in the RP and OCA groups. This reduction in activities due to OCA was greater in the B groups as compared to the A groups. A supplementation effect was seen in both groups. The per cent stimulation of EGOT was found to be greater in the OCA and RP groups. No socioeconomic or supplementation effect was seen so far as the EGOT stimulation test was concerned.

Table IV shows the results of erythrocyte and serum folate and vitamin B_{12}. Both plasma and red cell folate levels were higher in Group A than in Group B. A supplementation effect was seen in both groups. Erythrocyte and serum folate in the RP groups were higher than in the OCA groups.

Duncan's new multiple range test indicated that the A-RP subjects had higher red cell and serum folate levels than A-none subjects (Table V). Erythrocyte folate in A-1 and A-2 groups was decreased in comparison to that in subjects in A-none and A-RP groups. Serum folate in the A-2 group only was decreased when compared to A-none and A-RP groups.

Serum vitamin B_{12} levels in A-1 and B-1 groups were lower than those in A-2 and B-2 groups. No other significant differences were found with respect to serum vitamin B_{12} levels.

Comment

In the higher socioeconomic group, greater frequencies of abnormal clinical signs, indicative of malnutrition, were observed in OCA users as compared to control subjects. However, these signs, except for angular lesions of the mouth and debris or calculus of the teeth, were not observed in the lower socioeconomic group of OCA users. An increase in incidence of dental caries in OCA users of the higher socioeconomic group was also observed. In rats injected with OCA, elevated incidences of carious lesions proportional to increased doses of OCA have been reported by Liu and Lin.[14] Furthermore, these authors postulated that the increased dental caries activity of OCA-treated rats may be caused by a decrease in the plasma zinc concentration, since such a reduction has been observed in human subjects and rats receiving OCA.

The reduction in the PLP level due to OCA's was seen only in the upper socioeconomic group of subjects in this study. The subjects in the lower socioeconomic group did not show this effect. The fact that the reduction in EGOT activities due to OCA was greater in the lower than the upper socioeconomic group of subjects tended to support this finding. The activity of EGOT is dependent on the concentration of the coenzyme, PLP. Addition of PLP to the assay mixture

Table III. Levels of PLP and EGOT, and per cent stimulation of EGOT (mean ± S.D.)

Group		Plasma PLP (ng./ml.) S†	NS†	Avg.†	Total subjects
A-none		27.3 ± 15.2	12.6 ± 7.3	18.5 ± 13.1	25
A-1		9.5 ± 5.7	10.6 ± 4.6	10.3 ± 4.9	14
A-2		11.7 ± 8.6	7.8 ± 2.8	9.0 ± 6.3	16
A-RP		6.2 ± 5.1	6.6 ± 3.0	6.3 ± 4.8	65
B-none		9.3 ± 4.3	11.3 ± 5.7	10.9 ± 5.5	29
B-1		6.1 ± 3.0	11.9 ± 6.3	11.2 ± 6.3	25
B-2		7.6 ± 5.0	10.1 ± 4.0	9.9 ± 1.1	51
B-RP		12.3 ± 10.3	8.0 ± 3.7	10.0 ± 7.7	37
P values for treatment comparisons in analysis of variance	*Degree of freedom*				
P_1 = none vs. Norinyl, Ovral, and RP	1		0.001		
P_2 = RP vs. Norinyl and Ovral	1		0.001		
P_3 = Norinyl vs. Ovral	1		—		
Income (I)	1		—		
Supplement (S)	1		0.05		
Interactions	10				
I × P_1	1		0.001		
I × P_2	1		0.01		
S × P_1	1		0.01		
I × S	1		0.025		
I × S × P_1	1		0.01		
I × S × P_2	1		0.025		

*Raitman-Frankel units per milliliter of plasma on a basis of 45 per cent hematocrit.
†S, Supplemented; NS, nonsupplemented; Avg., average.

Table IV. Levels of erythrocyte and serum folic acid and serum B_{12} (mean ± S.D.)

Group		Erythrocyte folic acid (ng./ml.) S	NS	Avg.	Total subjects
A-none		318 ± 170	264 ± 107	295 ± 150	102
A-1		204 ± 77	175 ± 56	135 ± 64	28
A-2		253 ± 119	197 ± 107	208 ± 110	36
A-RP		457 ± 313	260 ± 165	430 ± 304	88
B-none		230 ± 81	181 ± 73	192 ± 77	63
B-1		222 ± 160	200 ± 91	204 ± 107	55
B-2		199 ± 83	172 ± 65	176 ± 69	106
B-RP		263 ± 214	234 ± 160	214 ± 180	82
P values for treatment comparisons in analysis of variance	*Degree of freedom*				
P_1 = None vs. Norinyl, Ovral, and RP	1		—		
P_2 = RP vs. Norinyl and Ovral	1		0.001		
P_3 = Norinyl vs. Ovral	1		—		
Income (I)	1		0.001		
Supplement (S)	1		0.001		
Interactions	10				
I × P_2	1		0.01		

EGOT (RF units*)				% Stimulation of EGOT			
S	*NS*	*Avg.*	*Total subjects*	*S*	*NS*	*Avg.*	*Total subjects*
4.01 ± 1.86	2.83 ± 1.02	3.61 ± 1.71	82	132 ± 76	163 ± 91	143 ± 82	81
2.43 ± 1.97	3.70 ± 2.57	3.41 ± 2.43	13	252 ± 115	188 ± 174	203 ± 160	13
3.37 ± 0.06	3.21 ± 1.61	3.25 ± 1.40	13	162 ± 40	166 ± 136	165 ± 119	13
3.87 ± 2.16	3.35 ± 1.81	3.57 ± 1.81	7	117 ± 33	200 ± 139	164 ± 109	7
4.55 ± 2.16	4.08 ± 1.75	4.20 ± 1.83	33	104 ± 52	129 ± 87	123 ± 80	33
3.79 ± 2.79	2.85 ± 1.08	3.04 ± 1.57	40	186 ± 145	156 ± 74	162 ± 92	39
3.34 ± 2.18	2.67 ± 1.29	2.79 ± 1.48	39	154 ± 137	204 ± 124	196 ± 126	37
3.50 ± 2.51	3.82 ± 2.63	3.73 ± 2.57	41	167 ± 118	165 ± 138	165 ± 131	41
	0.05				0.01		
	0.06				—		
	—				—		
	—				—		
	0.05				—		
	0.02				—		
	—				—		
	—				—		
	—				—		
	—				—		

Serum folic acid (ng./ml.)				Serum B_{12} (pg./ml.)			
S	*NS*	*Avg.*	*Total subjects*	*S*	*NS*	*Avg.*	*Total subjects*
6.59 ± 4.67	5.84 ± 3.77	6.30 ± 4.33	107	469 ± 172	446 ± 176	457 ± 172	28
4.47 ± 1.19	4.71 ± 2.50	4.62 ± 2.04	18	350 ± 127	290 ± 102	315 ± 113	17
4.92 ± 3.11	4.47 ± 3.15	4.55 ± 3.09	27	590 ± 433	461 ± 256	482 ± 279	19
7.72 ± 5.86	5.89 ± 5.23	7.50 ± 5.79	83	435 ± 173	679 ± 642	464 ± 273	60
4.20 ± 1.93	3.34 ± 1.24	3.53 ± 1.45	54	416 ± 72	521 ± 232	499 ± 212	38
4.41 ± 3.48	4.02 ± 1.64	4.09 ± 2.01	49	385 ± 125	378 ± 221	380 ± 204	22
4.79 ± 2.18	3.84 ± 1.30	3.96 ± 1.45	79	487 ± 201	478 ± 270	479 ± 259	67
6.43 ± 6.78	3.86 ± 1.89	4.73 ± 4.33	72	452 ± 274	478 ± 246	466 ± 255	36
	—				—		
	0.025				—		
	—				0.01		
	—				—		
	—				—		
	—				—		

Table V. Duncan's new multiple range test* for erythrocyte and serum folic acid in OCA users ($P < 0.05$)

Folic acid	*A-RP*	*A-none*	*B-RP*	*A-2*	*B-1*	*B-none*	*A-1*	*B-2*
Erythrocyte (ng./ml.)	430	295	244	208	204	192	185	176
	A-RP	A-none	B-RP	A-1	A-2	B-1	B-2	B-none
Serum (ng./ml.)	7.50	6.30	4.7	4.6	4.55	4.09	3.96	3.53

*Any two means not underscored by the same line are significantly different. Any two means underscored by the same line are not significantly different.

increases the activity of EGOT. The activation is related inversely to the concentration of PLP in the red cells and so may serve as an additional indicator of the vitamin B_6 status of the subjects. The per cent stimulation of EGOT was higher in the OCA and RP subjects in both socioeconomic groups in our study, suggesting a relative deficiency of the vitamin in those subjects. This may indicate that the EGOT-stimulation test is a more sensitive index of alterations in vitamin B_6 status than plasma PLP or EGOT.

The reduction of erythrocyte and serum folate due to OCA's was observed mainly in the upper socioeconomic group of subjects. This was not seen in the lower socioeconomic group.

Our data are consistent with the hypothesis that the subjects in lower socioeconomic groups were already marginally deficient with respect to vitamin B_6 and folic acid and, as such, further reduction due to OCA's could not be detected by our assay. Although an effect of OCA's on the levels of vitamin B_6 and folate was observed in subjects of the upper socioeconomic group, the clinical significance of this observation is not clear. Further studies are needed in order to define the clinical importance of these changes.

In our study, groups of subjects resuming the "pill" after pregnancy (A-RP and B-RP) demonstrated mainly the effects of pregnancy inasmuch as they resumed OCA's within five weeks post partum and the blood was sampled at the first visit after the pill was started. Our data indicate that the A-RP group was relatively deficient in vitamin B_6 but adequate in folic acid, suggesting that nutritional intake of B_6 was inadequate in this group.

Impairment of glucose tolerance is an important abnormality found in some OCA users which may be related to vitamin B_6 deficiency. Increased resistance to insulin by peripheral tissues, such as parametrial adipose tissues and diaphragm muscle, in vitro and in vivo was found to be responsible for the impairment of glucose tolerance in experimental animals treated with OCA's.[15] Murakami[16] suggested that xanthurenic acid is capable of attaining a complex with insulin, thereby reducing its biological activity. Indeed, a small group of women in whom carbohydrate tolerance had become impaired while using OCA's improved after vitamin B_6 administration. Several investigators have suggested that large doses of vitamin B_6 should be added to OCA's indiscriminately. However, the administration of a coenzyme may increase apoenzyme synthesis, and this may enhance the plasma amino acid–lowering effect of OCA's, which may produce an untoward effect in communities where protein malnutrition exists. At present, it would appear that the idea of supplementation of B_6 should be approached cautiously since the long-term effect of such therapy is uncertain.

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Endometrial suction biopsy: Appraisal of a new instrument

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With the use of a completely self-contained, pre-evacuated, and disposable suction apparatus, endometrial suction biopsy was performed in 250 patients presenting with abnormal uterine bleeding or for an infertility evaluation. The instrument's components and performance features are described, as well as the distribution of tissue diagnoses. Biopsy provided tissue sufficient for diagnosis in 90 per cent of cases where tissue was obtained. In the postmenopausal subgroup, hyperplastic transformation was seen in 28/71 (39 per cent) women, and occult adenocarcinoma was diagnosed in another nine (12 per cent). Over-all instrument performance was very good.

COMPARED WITH cervical cancer, carcinoma of the endometrium and its precursors until recently have received insufficient clinical attention.

Recent retrospective reviews have focused sharper attention upon the apparent increased risk of endometrial carcinoma, for example, in women receiving exogenous estrogens[1, 2] and even in young women using oral contraceptives.[3]

The advent of safe, reliable, and economic office techniques which can obtain tissue biopsies for endometrial cancer screening would be expected to increase measurably the number of early diagnoses. We have employed one of these instruments* to perform endometrial biopsy in 250 office patients. This report summarizes our experience predominantly in women presenting with abnormal bleeding.

Instrument

The Vakutage instrument is a totally disposable, completely self-contained, and pre-evacuated suction apparatus. Its three components include a cannula/curet, cap/sliding valve assembly, and glass collection bottle (Fig. 1). The clear, semiflexible cannula/curet, distally angled and calibrated, is available in sizes from 3 to 10 mm. When the slide valve is opened after intrauterine insertion, an instant and constant high vacuum is produced and maintained throughout the procedure. With the pressure-volume relationships embodied in this unit, vacuum does not decrease appreciably until the fluid-tissue volume aspirated reaches about 70 per cent of the collection bottle volume, affording more than adequate reserve for the procedure. The pre-evacuated glass collection bottle contains a transparent plastic trap vial, in which the tissue collects. After the procedure, this vial is detached, filled with the tissue preservative, and used as a specimen mailer.

Study population

Suction biopsy was performed in 250 women from the private practice of senior author (R.M.I.); all but four were Caucasian. Ages ranged from 16 to 81 years (average 41.3 years). Except for six women who had biopsies as part of an infertility evaluation, clinical indication for biopsy in this series was a presenting finding of abnormal uterine bleeding. Of these 244 women, 71 presented with bleeding following at least one year of postmenopausal amenorrhea. The remaining 173 represented apparent dysfunctional uterine bleeding.

For these 250 cases, local anesthesia was required in only two patients, and mechanical cervical dilatation was

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necessary in only seven instances. A 4 mm. cannula/curet was used in 218 cases; a 3 mm. size, in 11 women with a nulliparous or postmenopausal small cervical os; and a 6 mm. size, in 21 women with more patulous cervices.

Results

In order to contrast biopsy findings by age group and presence or absence of bleeding, tissue diagnoses are arranged in Table I into four categories: infertility patients and three groups of approximately equal size, including women 16 to 35 years old, premenopausal women 36 years old and older, and women with postmenopausal bleeding.

In the women undergoing infertility evaluation, tissue diagnoses revealed the usual spectrum of cyclic endometrial changes. Such was also the case with the women under 36 years old who presented with abnormal bleeding, except for some pregnancy-related events and hyperplastic changes which occurred in 14 of these 80 (17.5 per cent) patients. Hyperplastic changes in this group were generally mild in nature, and none was associated with concomitant estrogen therapy.

In the group over 36 years old with abnormal bleeding, hyperplastic changes were found in 33/93 (35.5 per cent) biopsies, and adenoacanthoma was diagnosed in one; only five of these women were receiving concomitant estrogen therapy. Endometrial polyps were removed in two cases, representing to us an advantage of this type of instrument over the classic nonsuction biopsy curet.

The extent and degree of adenomatous hyperplastic changes were more severe in the perimenopausal women and in the postmenopausal group. In the latter group of 71 biopsies, hyperplasia was seen in 28 (39.4 per cent) specimens, and adenocarcinoma was diagnosed in another nine (12.7 per cent). Forty-three of these 71 women (61 per cent) were receiving concomitant oral estrogens, including 21 of the 28 with biopsies showing hyperplasia and four of the nine with biopsies revealing carcinoma.

No tissue could be obtained in five of the 250 (2.0 per cent) of the procedures, and tissue insufficient for diagnosis was noted in 23 of the 250 (9.2 per cent) samples. The majority of these "failures" occurred in older postmenopausal women; in our opinion, it is unlikely that any alternative biopsy procedure would have been more fruitful. Over all, adequate biopsies were obtained in 222 of the 245 (90.6 per cent) cases where tissue was available.

The quality of the excised tissue was satisfactory and revealed good cellular preservation and nuclear detail; there was no artifactual distortion of the suctioned biopsy tissue.

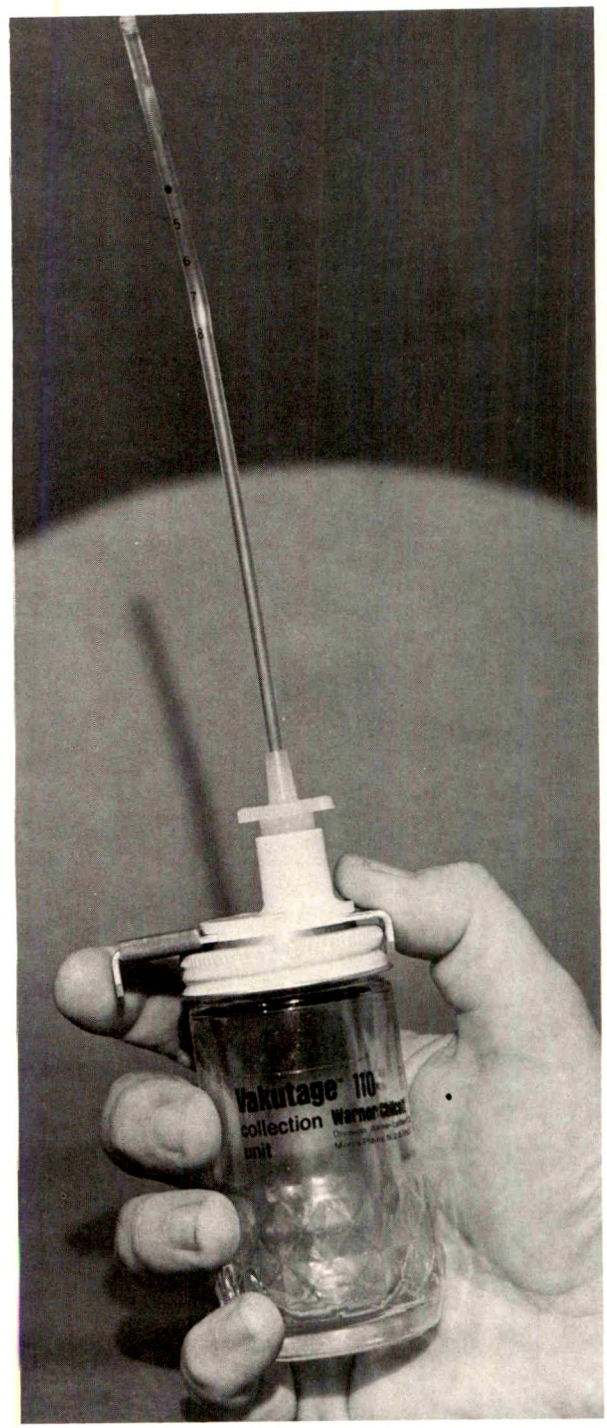


Fig. 1. Vakutage apparatus.

To date, 19 of these procedures have been followed by curettage or hysterectomy. Correlation with previous biopsy diagnosis has been very good with two exceptions; in one case, insufficient tissue on biopsy was followed by a diagnosis of cystic adenomatous

Table I. Clinical indication, age of patient, and diagnosis for 250 endometrial biopsies

	Patient group				
	Infertility	*Abnormal bleeding: Ages 16-35*	*Abnormal bleeding: Ages 36+*	*Postmenopausal*	*Total series*
No. of patients	6	80	-93	71	250
Age range	20-28	16-35	36-54	46-81	16-81
Average age	23.8	26.4	45.3	58.3	41.3
Endometrial pathology					
Proliferative	3	22	27	4	56
Secretory	2	20	10	0	32
Menstrual	0	5	3	2	10
Nonsecretory	1	4	6	2	13
Mixed proliferative secretory	0	1	2	0	3
Interval	0	0	1	0	1
Atrophic	0	0	1	3	4
Endometrial polyp	0	1	1	0	2
Endometritis	0	2	0	0	2
Myometrium	0	1	0	0	1
Hyperplasia					
Focal changes	0	4	6	2	12
Cystic glandular hyperplasia	0	4	4	11	19
Adenomatous endometrial hyperplasia	0	6	-22	11	39
Atypical endometrial hyperplasia	0	0	1	4	5
Adenoacanthoma	0	0	1	0	1
Adenocarcinoma	0	0	0	9	9
No malignant tissue	0	0	2	3	5
Decidual tissue/reaction	0	5	1	0	6
Products of conception	0	4	1	0	5
Insufficient tissue	0	2	4	17	23
No tissue obtained	0	0	2	3	5
Total No. of diagnoses	6	81	95	71	253*

*Three biopsies revealed two separate diagnoses.

hyperplasia at curettage, and in the other case the hysterectomy specimen revealed a well-differentiated adenocarcinoma whereas previous biopsy had shown only adenomatous hyperplasia.

Eight of the 250 (3.2 per cent) women experienced mild discomfort, e.g., transient cramps.

Comment

The Vakutage instrument was safe and effective in the performance of endometrial biopsy. It was easily held and manipulated with one hand. The prepackaged vacuum source is convenient in offices having several treatment rooms since there are no suction attachments needed. Performance characteristics of the cannula/curet were similar to those of conventional metallic biopsy cannulas with the advantage of transparency plus a slight degree of flexibility, which minimizes the risk of trauma but not at the expense of losing the sensation of intrauterine spatial placement, characteristic of firm instruments and lacking in soft plastic catheters.

From the diagnostic viewpoint, the advantages and limitations of endometrial biopsy for this instrument are similar to those of other biopsy modalities. However, the safety, ease of manipulation, tissue quality, and high degree of patient acceptance noted with this instrument can more firmly establish endometrial biopsy in the mind of the patient and physician as an indicated procedure in the management of abnormal uterine bleeding—especially in perimenopausal and postmenopausal women, including those receiving exogenous estrogens. Our findings of impressively large incidences of hyperplastic changes and carcinoma in these perimenopausal and postmenopausal patients support the more routine use of office endometrial biopsy. In women at high risk for endometrial carcinoma, we will need to consider more seriously routine screening for this disease and its precursors.

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Each tablet contains a low dosage of progestin, 1 mg norethindrone, and a low dosage of estrogen, 0.05 mg mestranol. Clinical studies with Ortho-Novum 1/50 show a pregnancy rate of only 0.26 per 100 woman years.

Low incidence of minor side effects† Experience shows a low incidence of discontinuance due to medication.

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†Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

most women who start with stay with

Ortho-Novum 1/50

Each yellow tablet contains 1 mg norethindrone and 0.05 mg mestranol. TRADEMARK □ 21 and
Each green tablet in the 28-day regimen contains inert ingredients.



See Prescribing Information on following page.

*TRADEMARK
††Burke Marketing Research, Inc.
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OJ 277-6

Most women who start with it stay with it



Ortho-Novum 1/50 ☐21 and 28

TRADEMARK

Ortho-Novum 1/50 ☐21 and Ortho-Novum 1/50 ☐28

Description: Each ORTHO-NOVUM 1/50 ▫21 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol.

Each yellow ORTHO-NOVUM 1/50 ▫28 Tablet contains 1 mg of the progestational substance, norethindrone, together with 0.05 mg of the estrogenic compound, mestranol. Each green tablet contains inert ingredients.

Actions: ORTHO-NOVUM 1/50 ▫21 and ORTHO-NOVUM 1/50 ▫28 act through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of ORTHO-NOVUM 1/50 ▫21 and ORTHO-NOVUM 1/50 ▫28.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May, 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 1.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28. Therefore, if such tests are abnormal in a patient taking ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 may mask the onset of the climacteric. 10. The pathologist should be advised of ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during ORTHO-NOVUM 1/50 ▫21 or ORTHO-NOVUM 1/50 ▫28 therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post-partum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol-extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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Articles to appear in early issues

Outpatient evaluation of patients with atypical Papanicolaou smears: Contribution of endocervical curettage
Hugh M. Shingleton, M.D., Hazel Gore, M.B., B.S., and J. Max Austin, Jr., M.D.
Birmingham, Alabama

The effect of L-dopa and chlorpromazine on prolactin and growth hormone secretion in normal women
H. Leblanc and S. S. C. Yen
La Jolla, California

Circulatory and cellular immune responses to squamous cell carcinoma of the uterine cervix
Wen Tsuo Chiang, Ping Yen Wei, and E. Russell Alexander
Seattle, Washington

Ovarian morphology in women with anosmia and hypogonadotropic hypogonadism
R. L. Goldenberg, R. D. Powell, Saul W. Rosen, John R. Marshall, and G. T. Ross
Bethesda, Maryland

Dysgerminoma of the ovary: Radiation therapy for recurrence and metastases
Muhammad Ali Afridi, M.D., Vitune Vongtama, M.D., Yoshi Tsukada, M.D., and M. Steven Piver, M.D., F.A.C.O.G.
Buffalo, New York

Reported live births following induced abortion: Two and one-half years' experience in Upstate New York
George Stroh and Alan R. Hinman, M.D.
Albany, New York

Antepartum fetal heart rate and uterine activity studies. I. Preliminary report of accelerations and the oxytocin challenge test
H. E. Fox, M.D., M. Steinbrecher, B.S., and B. Ripton, B.S.N.
Rochester, New York

Asymptomatic bacteriuria in pregnancy: Antibody-coated bacteria, renal function, and intrauterine growth retardation
Robert E. Harris, M.D., Ph.D., Virginia L. Thomas, Ph.D., and Alexis Shelokov, M.D.
Lackland Air Force Base and San Antonio, Texas

Systolic time intervals in normotensive and hypertensive human pregnancy
Y. L. Lim, B.Med.Sc., M.B., B.S., and W. A. W. Walters, M.B., B.S., Ph.D., F.R.C.O.G., F.A.G.O.
Melbourne, Victoria, Australia



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1. Bonnar, J., et al., Lancet, 1:457, 1969.
2. Porter, A. M. W., Brit. Med. J., 1:218, 1969.

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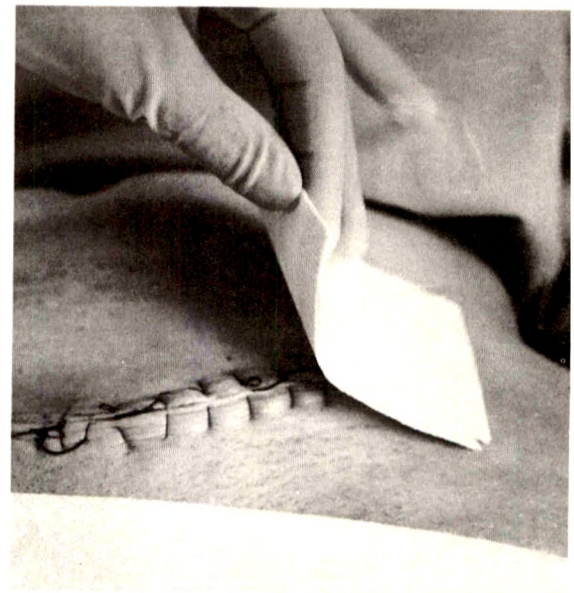
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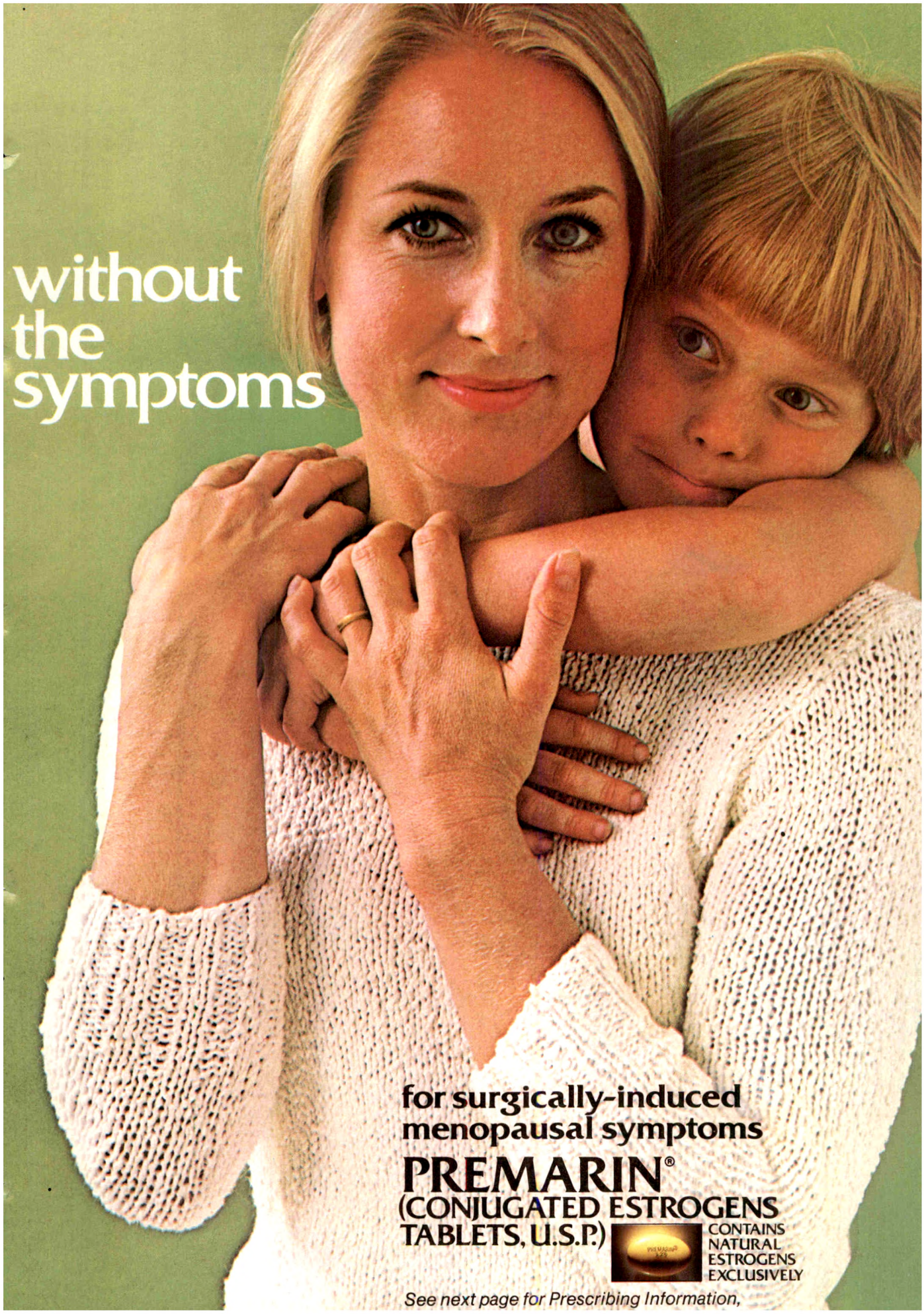
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Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (*e.g.* anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration; however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)
No. 865—Each *purple* tablet contains 2.5 mg, in bottles of 100 and 1,000.
No. 866—Each *yellow* tablet contains 1.25 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 867—Each *red* tablet contains 0.625 mg, in bottles of 100 and 1,000. Also in unit dose package of 100.
No. 868—Each *green* tablet contains 0.3 mg, in bottles of 100 and 1,000.

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SYNTEX

Announcing an important new service program from Syntex --
designed specifically for the obstetrician/gynecologist

Dear Doctor:

The past two years have seen an increasing concern about the need for change and improvement in the traditional OB/GYN patient relationship.*

In seeking how we might help the specialty to maintain a close, positive relationship with women at a time of rapidly changing expectations, Syntex held a number of panel discussions with women all over the country. We asked them how they felt about their OB/GYN experiences. We got some telling answers.

We invited OB/GYNs at the Dallas ACOG meeting to listen at our booth to tapes from those panel discussions. Some 1,500 doctors, their spouses and nurses, enthusiastically took us up on that offer; you may have been one of them.

The result of those patient panels and our discussion with OB/GYNs made us realize that many of the problems of patient dissatisfaction and alienation were essentially problems in communication -- communication from the doctor and the office staff to the patient, communication from the patient to the OB/GYN team.

These problems, often minor, were producing strains in the doctor/patient relationship way out of proportion to their cause.

As a result of our research Syntex has now developed WHY PEOPLE COME BACK -- a continuing series of materials and counsel for improving communication in your practice.

Our aim was not to design an "academic" program, but one that would present practical, workable advice, forms and materials to

(over)

improve the total communication environment; a program that would cycle the experience, ideas and proven methods of OB/GYN health-care teams to their colleagues in the specialty.

We are pleased to announce the introduction of WHY PEOPLE COME BACK. We invite you to review the first materials in our on-going series when your Syntex representative calls on you. And we invite you to participate in the further development of the program, since we intend it to be responsive to the needs of practicing OB/GYNs like yourself.

It is Syntex's privilege to serve as a communication link between OB/GYN teams and we welcome your criticism, thoughts and ideas on how we might best help you with effective communication, an important part of the art of medicine.

Sincerely,

Richard G. Rogers
President

* References:

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OBSTETRICS

Endocrine-metabolic response to acute starvation in human gestation

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During a 72 hour fast in pregnant women, significant decrements in the maternal plasma glucose concentrations, accompanied by a significant increase in the plasma placental lactogen (hPL) concentration, occur. At the same time, utilization of glucogenic amino acids, principally alanine, takes place. The mean postprandial glucose concentration in pregnancy is significantly lower than that of comparable nonpregnant women (70.5 ± 1.7 versus 79.5 = 1.3 mg. per 100 ml., $p < 0.001$). There appears to be a significant sparing effect on the maternal plasma glucose concentration during acute fasting which may be mediated through hPL. Concentrations of amniotic fluid and fetal plasma glucose from women undergoing fasting decrease in a manner parallel to that of the mother. Fasting provokes a mean rise in plasma hPL of 33.2 per cent over basal levels. This rise is still evident 72 hours after refeeding, after which it gradually returns to pretest concentrations. The infusion of alanine or arginine to pregnant women at the end of the fast produced increments in the peripheral maternal glucose concentration. The response was much greater with alanine than with arginine, demonstrating the increased gluconeogenic potential of this amino acid. The increment in human growth hormone (hGH) following alanine infusion was significantly greater than that observed after arginine administration. Hypoaminoacidemia was present in nonpregnant and pregnant women in response to fasting, but the decline was greater in pregnancy. Acute fasting in the first half of gestation appears to produce significant alterations in carbohydrate metabolism evidenced by profound hypoglycemia, hypoinsulinemia, and hypoaminoacidemia. This maternal deficit can be reflected in fetal substrate concentrations. The effect of these changes on fetal growth and development is speculative at this time.

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PROLONGED FASTING in the first half of human gestation is accompanied by exaggerated maternal hypoglycemia,[1, 2] accompanied by a rapid depletion of maternal hepatic glycogen stores prior to amino acid mobilization from the muscle.[3] During this time, a rise in the peripheral concentration of human placental lactogen (hPL) has been observed.[1, 4]

It has been postulated that gluconeogenesis, under conditions of prolonged fasting, is accomplished by the utilization of glucogenic amino acids, principally alanine.[5, 6] and that this amino acid is more rapidly

Table I. Subject data

Data	Pregnant	Nonpregnant
No.	24	41
Age (years)	18-29	18-23
Duration of pregnancy (weeks)	8-20*	—
Mean body weight (kilograms)	62.2 ± 1.4†	60.7 ± 1.6
Mean weight loss (kilograms) during fast	3.1 ± 0.1	3.2 ± 0.1

*Twenty-four of 27 women.

†No one was > ± 5 per cent of the ideal body weight based upon Metropolitan Life Insurance tables from 1959.

depleted during fasting in pregnancy.[3] More recent evidence suggests that the stabilization of the plasma glucose concentration in fasting pregnant women must occur at the expense of substrate utilization other than alanine and that hPL plays a role in this mechanism.[7]

That hypoglycemia in response to fasting in pregnancy is lower than in comparable nonpregnant control subjects was reported by Felig and associates.[8] Yet the exaggerated human growth hormone (hGH) secretion observed in response to amino acid infusion and protein meals during the first half of gestation made uncompensated hypoglycemia seem improbable.[9, 10]

The present study was designed to evaluate more extensively the maternal endocrine-metabolic adjustments which ensue during prolonged nutritional deprivation in the first half of pregnancy and to examine the response of plasma glucose, insulin, and hGH concentrations to the infusion of two glucogenic amino acids.

Methods

Study population. Pregnant women in the first half of gestation were approved for therapeutic abortion by a committee within the Department of Gynecology and Obstetrics of The Johns Hopkins Medical Institutions. Once the date for the operative procedure was confirmed, interviews were conducted to determine a woman's willingness to participate in the research protocol. The hazards of such participation were clearly explained, and informed consent was obtained independent of any other consent necessary for the abortion procedure. The entire project was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins University School of Medicine.

Twenty-seven healthy, nonobese, pregnant women fasted for 72 hours prior to abortion. Of these, 24 were studied between the eighth and twentieth weeks of gestation while three women, known to be carrying fetuses with congenital malformations incompatible with extrauterine life (anencephaly), were studied between the twenty-sixth and thirty-sixth weeks of gestation. All procedures related to fasting were completed at least 12 hours prior to the definitive abortion procedure.

A group of 41 healthy, nonobese, nonpregnant women served as control subjects. None had historical evidence of endocrine disorders or hepatic dysfunction. None had ever been pregnant and were not ingesting oral contraceptives prior to the study. The group was further subdivided depending upon the menstrual interval in which fasting occurred. The plasma glucose results from these subgroups have recently been reported.[11]

Vital statistics on both main groups are presented in Table I. Not included are the values for the three women who fasted between the twenty-sixth and thirty-sixth weeks of gestation.

Study protocol. All studies were performed in the Clinical Research Center of the Johns Hopkins Hospital. Caloric intake for the week prior to the study was calculated to represent a balanced diet of no less than 2,200 calories daily. Each fast was started on a Thursday, beginning at 8:00 P.M., immediately following the ingestion of the evening meal. Studies were uniformly completed 72 hours later. During the fast, intake was limited to a multiple vitamin capsule and water ad libitum. Light activity was encouraged in all volunteers. With the women at rest for at least 30 minutes prior to sampling, blood was drawn through an antecubital vein precisely at 8:00 A.M. and again at 4:00 P.M. daily. Additional samples were drawn at 8:00 P.M. (72 hours) on the third day. Each sample was collected in a tube containing heparin, and the plasma was separated by centrifugation and stored at −20° C. until assayed.

Women from each group were selected at random to receive one of two metabolic substrates immediately following the fast. Ten grams of L-alanine or 30 Gm. of L-arginine was infused intravenously over a 30 minute period in order to determine the glucogenic potential of each substrate as measured by changes in the peripheral glucose and insulin concentrations. Blood samples for these studies were obtained at 0, 5, 10, 15, 30, 60, and 90 minutes through an indwelling needle in an antecubital vein. All volunteers were refed following the final blood sample either at 72 hours or after the completion of an infusion study.

Abortion in 17 women was performed with transabdominal instillation of hypertonic saline. Two women were aborted by suction curettage, and five underwent hysterotomy. In cases were amniocentesis was per-

Table II. Mean plasma glucose and insulin concentrations in healthy pregnant and nonpregnant women during a 72 hour fast

	Hours of fasting				
Women	*12*	*20*	*36*	*60*	*72*
Nonpregnant (No. = 41)					
Glucose (mg./100 ml.)	79.5*	70.4	56.1	47.1	45.8
	±1.3	±1.3	±1.9	±2.0	±1.2
Insulin (μU/ml.)	11.9	10.0	6.8	3.7	3.6
	±0.9	±1.9	±1.0	±0.7	±0.5
Pregnant (No. = 24)					
Glucose (mg./100 ml.)	70.5	63.2	51.9	49.7	50.2
	±1.7	±2.3	±2.3	±1.8	±1.6
	($p < 0.001$†)	($p < 0.01$)			($p < 0.05$†)
Insulin (μU/ml.)	7.7	5.4	3.9	5.6	4.9
	±0.8	±0.7	±0.5	±0.8	±0.9
	($p < 0.001$)	($p < 0.001$)	($p < 0.01$)		

*Mean ± standard error.

†Statistical comparison with comparable nonpregnant control values.

formed, ultrasonic localization of the placenta was utilized. With local intradermal anesthesia, a No. 19 gauge needle was inserted through the abdominal wall and into the amniotic sac from which a minimum of 15 ml. of amniotic fluid was withdrawn. Subsequent samples were drawn from different abdominal sites.

Glucose analysis. Both plasma and amniotic fluid glucose (AFG) concentrations were measured by the glucose oxidase method of Huggett and Nixon.[12]

Plasma hormone analyses. Plasma hPL was measured by a modification of the method described by Schalch and Parker,[13] while hGH was measured by the method of Roth and associates.[14] Antisera of sufficiently high specificity was used in the hGH assay so that cross-reactivity with hPL was negligible. Plasma insulin was measured by the radioimmunoassay method of Herbert and colleagues.[15] Plasma human prolactin (hPRL) was measured with a homologous double-antibody radioimmunoassay modified from the method of Hwang and co-workers.[16]

Amino acid analysis of plasma and amniotic fluid. Plasma, deproteinized with sulfosalicyclic acid, was stored at −20° C. until analyzed for amino acid content on an amino acid analyzer.* Chromatographic separation of the amino acids was accomplished with sodium citrate buffers. Amniotic fluid amino acids (AFAA) were analyzed in a similar manner.

Urinary determinations. Aliquots from 24 hour collections were frozen and stored at −20° C. until analyzed for amino acids.[17]† Urine samples were thawed and centrifuged, and a volume of 10 to 150 μl of the supernatant was subjected to electrophoresis. The actual volume used for each sample was based on the urinary creatinine determination. This technique was specific for separating basic and acidic amino acids from the neutral group. The portion of the electrophoretogram containing the neutral amino acids was subjected to ascending chromatography to complete the separation of these amino acids. All portions of the electrophoretogram and the chromatogram

Table III. Mean plasma hGH and hPRL (nanograms per milliliter) in pregnant and nonpregnant women during a 72 hour fast

	Hours of fasting			
	12	*36*	*60*	*72*
Nonpregnant (No. = 41)				
hGH	2.4*	6.2†	4.6†	3.6
	±0.6	±1.3	±0.6	±0.6
hPRL	15.8	15.6	14.9	13.5‡
	±1.1	±1.2	±1.6	±1.5
Pregnant (No. = 24)				
hGH	2.1	5.7†	4.8§	3.6
	±0.8	±1.2	±1.0	±1.5
hPRL	101.4	98.6	94.7	80.2‖
	±20.7	±21.1	±18.8	±17.2

*Mean ± standard error.

†$p < 0.02$ as compared to 12 hour value with nonpaired Student's t test.

‡$p < 0.05$ as compared to 12 hour value with paired Student's t test.

§$p < 0.05$ as compared to 12 hour value with nonpaired Student's t test.

‖$p < 0.01$ as compared to 12 hour value with paired Student's t test.

*C-121, Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, California 92634.

†These determinations were performed by Dr. Neil Holtzman.

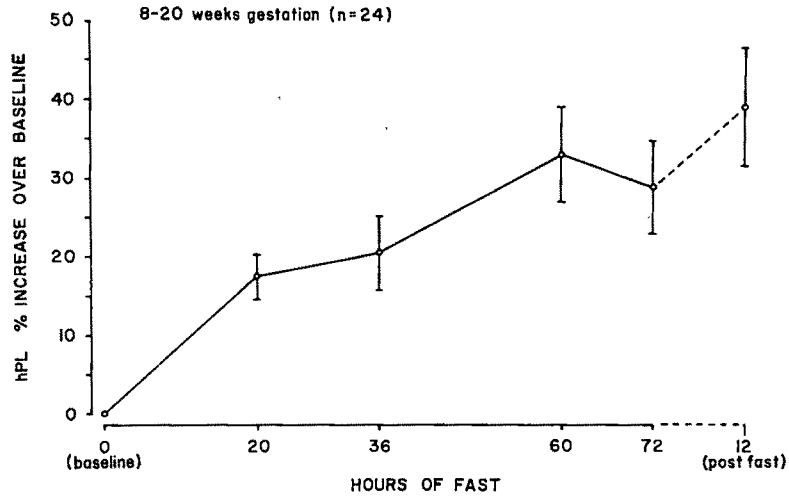


Fig. 1. Per cent increment in plasma hPL during fasting in women between 8 and 20 weeks' gestation.

were stained with ninhydrin, after which the quantity of each amino acid was determined by densitometer measurement.

Urinary urea nitrogen was measured on a 6/60 Sequential Multiple Analyzer with a modification of the method of Marsh and associates.[18] Urinary creatinine was measured on a Dynacon with the use of the Jaffe reaction. The method of Kaplan[19] was used for the determinations of urinary ammonia.

Statistical analysis. Statistical analyses were performed with the Student's t test used for paired and nonpaired data and the rank correlation of paired data.

Results

Plasma glucose and insulin concentrations. The maternal plasma glucose concentration as compared to that in nonpregnant control subjects was significantly lower in the postabsorptive state (12 hours), as shown in Table II. By 72 hours of fasting, the mean plasma glucose in control subjects fell 33.7 mg. per 100 ml. compared to a mere 20.3 mg. per 100 ml. in pregnant women. The greatest decline occurred between the twelfth and the sixtieth hours in both groups, after which a further slight decline in the plasma glucose concentration was observed in control subjects. The mean 12 hour postprandial glucose concentration after refeeding was 86.6 ± 3.7 mg. (S.E.M.) per 100 ml. for control subjects compared to 77.2 ± 5.3 mg. per 100 ml. for pregnant women ($p < 0.001$). As reported previously, no significant difference in plasma glucose values was observed between women who fasted early or late in the menstrual cycle.[11]

The fall in the plasma insulin concentration was closely related to the fall in plasma glucose. A rank correlation between plasma glucose:insulin ratios in control and pregnant women was significantly different ($T = 2.5076$, $p < 0.001$) at 12, 36, 60, and 72 hours, confirming that the fall in plasma insulin is directly proportional to the net decrease in the plasma glucose concentration. A continued positive rank correlation was observed in the plasma glucose:insulin ratios at 12 hours after feeding. During the follicular phase of the menstrual cycle, the mean plasma insulin concentration fell from 7.1 ± 0.9 to 3.1 ± 0.8 μU per milliliter (No. = 19) after 72 hours of fasting and from 9.4 ± 1.2 to 3.8 ± 0.8 μU per milliliter in women during the postovulatory phase (No. = 22).

Plasma hGH and hPRL levels during fasting. Mean basal plasma hGH levels of the groups were not significantly different, as shown in Table III. A consistent rise in the mean basal hGH level occurred between 12 and 36 hours in each group ($p < 0.02$). Peripheral hPRL levels are known to rise during normal gestation; therefore, the difference between basal hPRL concentrations of the two groups in this study represents a normal gestational effect. On the other hand, a consistent fall in plasma hPRL was noted in both the pregnant and control women during the fasting period which was significant at 72 hours.

Plasma hPL responses to prolonged fasting in gestation. Consistent with our previous observation,[1] the mean plasma hPL concentration rose during short-term fasting. Plasma hPL was measured on two occasions 15 minutes apart in women confined to the recumbent position for 30 minutes during the twelfth hour of the fast. The mean of these values constituted the basal hPL determination. All subsequent values

Table IV. Mean plasma amino acids in healthy nonpregnant women during a 72 hour fast (No. = 10)

Amino acid	*Duration of fast (hr.)*				*Significance†*
	12	*36*	*60*	*72*	
Aspartic acid	11.2*	7.5	9.7	13.5	
	±0.7	±0.7	±0.7	±3.0	N.S.
Threonine	123.4	96.5	99.9	112.5	
	±8.3	±7.5	±8.3	±10.0	N.S.
Serine	152.2	125.5	128.4	153.1	
	±11.4	±9.5	±9.5	±9.5	N.S.
Glycine	211.7	143.8	134.4	170.4	
	±19.9	±14.6	±11.9	±15.9	N.S.
Alanine	292.9	209.8	188.5	227.8	
	±19.0	±14.5	±10.1	±12.3	<0.02
Valine	209.0	359.2	452.2	435.1	
	±9.3	±22.1	±23.0	±29.8	<0.001
Methionine	24.7	22.7	34.1	32.1	
	±0.6	±0.6	±2.6	±0.6	<0.001
Isoleucine	66.3	134.1	175.3	160.8	
	±2.2	±9.1	±9.9	±12.9	<0.001
Leucine	122.7	262.9	313.2	282.0	
	±6.0	±19.1	±19.1	±19.8	<0.001
Tyrosine	41.9	43.5	58.4	61.2	
	±2.2	±2.2	±3.3	±2.7	<0.001
Phenylalanine	43.5	47.2	54.4	63.5	
	±2.4	±3.0	±3.0	±3.0	<0.001
Lysine	119.1	120.5	117.8	157.5	
	±11.6	±13.6	±12.3	±7.5	<0.02
Histidine	75.9	61.0	68.1	92.8	
	±7.7	±9.7	±10.3	±4.5	N.S.
Arginine	107.3	86.6	88.9	101.0	
	±9.7	±6.8	±4.5	±13.7	N.S.

*Mean ± standard error.
†Significance of 72 hour value compared to 12 hour value with nonpaired Student's t test.
N.S. = Not significant.

were calculated as a per cent of that basal value. For the women between eight and 20 weeks' gestation, the per cent increment in plasma hPL during fasting is shown in Fig. 1. At 20 hours, the mean per cent increment in hPL was 17.5 ± 2.8 per cent and rose steadily to 33.2 per cent at 60 hours. A slight fall was observed at 72 hours but 12 hours later, after refeeding, the hPL concentration remained elevated. Measurements of hPL were made in four women for an additional 48 hours following the fast. The mean per cent increment during this time was somewhat lower at 14.2 per cent.

When the data are divided according to the weeks of gestation, the net hPL response in women between 8 and 14 weeks was 51.3 per cent at 72 hours compared to 21.2 per cent in women who fasted between 15 and 20 weeks' gestation. Minute increments in hPL (3.8 per cent) were observed in the three women who fasted between the twenty-sixth and thirty-sixth weeks of gestation.

The opportunity arose for observation of the effects of fasting in a pregnant woman who was found to be carrying a dead fetus at the sixteenth week of gestation. Based upon urinary pregnanediol concentrations, the placenta was considered to be viable. During the fast, the metabolic changes in terms of plasma glucose : insulin concentrations were identical to those just described. Moreover, plasma hPL rose 18.5 per cent within 24 hours and peaked at the sixtieth hour at 22 per cent. When aborted by hypertonic saline, the fetus was found to have no grossly detectable abnormalities.

Of importance to the interpretation of these results are the changes which occur in maternal hemodynamics. To the thirty-fourth week of gestation, the magnitude of the average increase in blood volume ranges from 20 to 85 per cent and so perhaps affects the absolute concentration of hPL. To test this hypothesis, aliquots of urine were processed in a manner similar to that for plasma and assayed for hPL. The mean urinary hPL in four women tripled between days 1 and 3 of the fast, suggesting that the plasma increment was real. The stability of the daily hematocrit and plasma protein value provided additional information to rule out a significant constriction of the intravascular volume as a reason for the elevated plasma hPL levels.

Alterations in plasma amino acid concentrations

Table V. Mean plasma amino acids in healthy, pregnant women during a 72 hour fast (No. = 10)

Amino acid	*Duration of fast (hr.)*				*Significance*
	12	*36*	*60*	*72*	
Aspartic acid	9.7* ±1.5 (N.S.†)	14.2 ±2.2	12.7 ±3.0	18.0 ±3.0	<0.05‡
Threonine	171.2 ±8.3 (<0.002)	151.1 ±12.5	174.6 ±18.4	216.6 ±41.9	N.S.
Serine	95.1 ±8.5 (<0.002)	105.6 ±9.5	114.1 ±10.4	177.9 ±16.1	<0.001
Glycine	107.8 ±6.6 (<0.001)	89.2 ±7.9	95.8 ±9.3	103.4 ±5.3	N.S.
Alanine	223.3 ±20.2 (<0.05)	163.8 ±14.5	141.3 ±13.4	167.2 ±8.9	<0.05
Valine	148.4 ±5.1 (<0.001)	238.9 ±11.0	279.8 ±18.7	292.6 ±45.2	<0.01
Methionine	20.7 ±1.3 (<0.02)	23.4 ±2.0	24.7 ±1.3	24.1 ±1.2	N.S.
Isoleucine	47.2 ±2.2 (<0.001)	82.3 ±5.3	95.2 ±7.6	102.8 ±22.8	<0.05
Leucine	84.6 ±3.0 (<0.001)	166.1 ±9.9	180.6 ±14.4	190.5 ±41.1	<0.05
Tyrosine	22.6 ±2.2 (<0.001)	25.3 ±2.2	28.6 ±2.7	40.8 ±4.4	<0.005
Phenylalanine	30.8 ±3.0 (<0.01)	33.2 ±3.6	36.3 ±3.0	49.0 ±3.6	<0.002
Lysine	83.5 ±11.6 (N.S.)	102.7 ±12.3	104.1 ±13.6	160.2 ±4.7	<0.001
Histidine	53.2 ±17.5 (N.S.)	35.7 ±11.6	49.3 ±15.5	88.3 ±11.6	N.S.
Arginine	66.0 ±6.3 (<0.005)	66.5 ±5.1	74.0 ±7.4	103.3 ±4.5	<0.001

N.S. = Not significant.

†Significance compared to 12 hour value in nonpregnant women with the use of nonpaired Student's t test.

‡Significance of 72 hour value compared to 12 hour value with the use of nonpaired Student's t test.

during fasting. While the methodology permits the measurement of individual amino acids in physiologic concentrations, it offers poor resolution of glutamic acid and glutamine. Thus, determinations of these levels were excluded from the study. Amino acid determinations were performed on plasma obtained twice daily throughout the fasting period. For statistical purposes, only values obtained at 12, 36, 60, and 72 hours of fasting were used.

Nonpregnant subjects. The plasma concentrations of aspartic acid, threonine, and serine remained constant while a slight fall in the concentration of glycine was observed, as seen in Table IV. Branched-chain amino acids, including the concentrations of tyrosine and phenylalanine, showed a marked rise. Plasma alanine fell rapidly, reaching a nadir at 60 hours with a rebound occurring at 72 hours. The net decrease was nevertheless significant. Plasma glycine was significantly lower ($p < 0.05$) at 60 hours but then rose an average of 36 μmoles per 100 ml. at 72 hours. Both lysine and histidine showed a modest rise. The plasma amino acid concentrations 12 hours after refeeding had returned to the initial postabsorptive levels.

Pregnant subjects. The postabsorptive amino acid concentrations in pregnant women are shown in Table V and are compared statistically to the values obtained at comparable time intervals in nonpregnant subjects. The 12 hour mean value for 11 of 14 amino acids was significantly lower during pregnancy. Further alterations in the concentrations of each amino acid were consistent with those observed in control subjects but were more exaggerated.

Alanine fell between 12 and 60 hours. Plasma arginine was higher at 72 hours in pregnant women. Since the concentration of histidine was comparable in pregnant and nonpregnant women, we have interpreted this to represent a relative hyperhistidinemia which has been reported previously.[8] Twelve hours after refeeding, alanine and glycine remained low.

Urinary excretion of amino acids and nitrogen (Tables VI and VII). The daily urinary volume was slightly greater in control subjects on the second and third days of fasting. Urinary urea nitrogen and ammonia excretion were comparable in both groups, suggesting no alteration in catabolic processes due to pregnancy. The aminoaciduria of early gestation[20] is

reflected in the changes in urinary alanine excretion shown in Table VII. Such changes were indistinguishable between groups, indicating unaltered renal clearance for this specific amino acid. On the other hand, glycine excretion fell precipitously in the pregnant subjects and, compared to plasma levels, implied an increased peripheral utilization of the substrate, perhaps at the renal level.

Amniotic fluid studies. The amniotic fluid represents a dynamic system of essential substrates, both hormonal and metabolic, between mother and fetus. Regrettably, fluctuations in amniotic fluid volume due to fetal urination and swallowing are difficult to equate with respect to the over-all exchange rate of amniotic fluid constituents. Attempts were made to obtain daily samples of amniotic fluid during the study.

The mean AFG concentration in 36 normal, fed women between the fourteenth and twentieth weeks of gestation was 25.0 ± 1.8 mg. per cent while the AFG from 13 normal pregnant women between 25 and 40 weeks' gestation was 15.5 ± 2.9 mg. per 100 ml. Since these mean concentrations were similar to those reported by Schreiner,[21] they were used as normal controls for the following studies.

Amniotic fluid was obtained from eight women at 24 hour intervals during the 72 hour fast. The mean amniotic fluid glucose in the first 24 hours was 20.1 ± 2.0 mg. per 100 ml but fell to 8.0 ± 1.2 mg. per 100 ml. at 72 hours. The AFG just prior to abortion and after feeding had rebounded to 40.1 mg. per 100 ml. suggesting that the changes in AFG in response to maternal fasting and refeeding may be sensitive enough to be used as an indicator of the fetal metabolic status. The fetal plasma glucose concentration in cord plasma from five fetuses at the time of hysterotomy in women who were not refed was 18.1 mg. per 100 ml., a value similar to the mean AFG concentration in these cases.

Amniotic fluid obtained from 10 women at the termination of their fast was analyzed for threonine, glycine, alanine, leucine, and arginine. The mean concentration of these amino acids are shown in Table VIII compared to values in amniotic fluid of fed women at the same stage of gestation and studied for a different purpose at the same time.[22] A 30 per cent fall in alanine and an 18 per cent fall in glycine was recorded in the fasting stage.

Metabolic effects of glucogenic substrates. As a principal gluconeogenic substrate, alanine is preferentially utilized in hepatic glycogen synthesis.[5] In pregnancy, however, the affinity of hepatic tissue for alanine and its subsequent utilization to glucose appears increased.[3] To further evaluate this, 10 Gm. of alanine in an isotonic solution of 300 ml. was administered intravenously to pregnant and control volunteers over a 30 minute interval immediately folllowing 72 hours of fasting. The mean plasma glucose, insulin and hGH concentrations are shown in Fig. 2.

The mean peak glucose concentration was achieved at 60 minutes in both groups with parallelism being

Table VI. Urinary parameters during fasting

Urinary parameter	*Day 1*	*Day 2*	*Day 3*
Volume (ml.)			
Pregnant (No. = 6)	1,333*	1,037	1,040
	±217	±228	±152
Nonpregnant (No. = 15)	1,371	1,413	1,421
	±130	±114	±93
Urea nitrogen (Gm./N_2)			
Pregnant (No. =13)	6.6	8.3	12.7
	±0.3	±0.1	±1.2
Nonpregnant (No. = 18)	5.9	7.8	12.5
	± 0.4	±0.4	±0.6
Creatinine (mg./vol.)			
Pregnant (No. = 13)	95.0	134.21	88.5
	±11.3	±20.9	±6.8
Nonpregnant (No. = 18)	132.2	136.7	101.9
	±14.2	±14.8	±8.2
Ammonia (mg./vol.)			
Pregnant	29.7	71.6	86.0
	±5.1	±8.7	±7.6
Nonpregnant	34.0	50.1	70.9
	±2.1	±7.1	±9.1

*Mean ± standard error.

Table VII. Urinary excretion of amino acids (micromoles per milligram of creatinine per 24 hours)

	Pregnant (No. = 13)			*Nonpregnant (No. = 5)*		
Amino acid	*Day 1*	*Day 2*	*Day 3*	*Day 1*	*Day 2*	*Day 3*
Alanine	195.0*	176.8	231.0	178.3	175.7	224.2
	±18.5	±21.2	±49.7	±11.2	±27.3	±28.8
Glycine	1,078.7	765.6	583.1 †	562.0	513.3	579.6
	±178.3	±121.5	±78.6	±43.0	±117.5	±108.6

*Mean ± standard error.

†$p < 0.05$ as compared to Day 1 with nonpaired Student's t test.

Table VIII. Mean amniotic fluid amino acids (micromoles per liter)

Amino acid	*Fasted (10)*	*Fed (36)*
Threonine	184	184
Glycine	146	173
Alanine	280	392
Leucine	70	85
Arginine	51	45

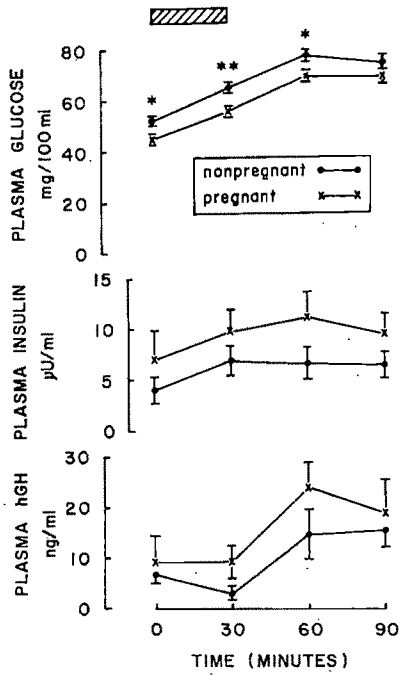


Fig. 2. Mean plasma glucose, insulin, and hGH concentrations in pregnant and control volunteers following the infusion of 10 Gm. of alanine at the end of a 72 hour fast.

noted at each sampling point. Nevertheless, the values were uniformly less in pregnant women. The net plasma insulin response was greater in pregnant women. While the plasma hGH response was marked in both groups, there was no change in the concentration of hPRL.

The results of arginine infusion are shown in Table IX. While all the nonpregnant women represented in this table were from the same pool of volunteers, they were merely matched for age and weight. None of the women receiving arginine at 12 hours fasted. On the other hand, the pregnant women were matched for age and stage of gestation. Those receiving arginine in the postabsorptive state did not participate in the prolonged fast since it was impossible to anticipate the effects of arginine from the subsequent values for glucose, insulin, and growth hormone during the remaining hours of the fast.

Studies in late pregnancy. Three women known to be carrying anencephalic fetuses at 26, 32, and 36 weeks' gestation fasted for three days prior to abortion. Changes in plasma amino acids, hGH, and insulin concentrations were similar to those described for the whole group. The fall in the mean plasma glucose concentration was more dramatic, reaching a nadir at 72 hours of 29.8 mg. per 100 ml, 35 per cent lower than the mean for the remaining women who fasted. Plasma hPL rose less than 5 per cent above the basal level as mentioned previously and, between 36 and 72 hours, the mean AFG fell from 18 to 1.2 mg. per 100 ml. The glucose concentration in fetal cord venous plasma was 1.2 mg. per 100 ml. in the 32 week fetus and undetectable in the plasma of the 36 week fetus delivered by hysterotomy. Postmortem examination of each fetus revealed the presence of an intact pituitary gland.

Comment

In a three-compartment system represented by maternal and fetal plasma and by amniotic fluid, profound hypoglycemia occurs in response to acute nutritional deprivation in the first half of human gestation and thereafter. At the same time, a significant depletion in the principal gluconeogenic substrate, alanine, is related to its role as a stabilizing influence on maternal fuel economy. Moreover, the efficiency of the system is greater than was previously thought[8, 23] based upon the net changes in the maternal plasma glucose concentration.

While Felig and colleagues[8] reported uncompensated maternal hypoglycemia in response to an 84 hour fast, our data suggest the presence of compensatory mechanisms predicated perhaps by a readjustment in hPL synthesis which is designed to preserve maternal glucose or even enhance gluconeogenesis. A comparison of fasting plasma glucose concentrations in nonpregnant women in our study with those of Felig and colleagues indicates that methodology was not responsible for the difference observed in the maternal values between the two studies.

In postulating an inordinate depletion of glucogenic substrates during fasting in pregnancy, several authors have suggested that this places the fetus at risk.[24, 25] However, recent studies in sheep and rats provide evidence of alternate pathways for fetal metabolism and fuel economy during prolonged maternal starvation.[26]

Our findings on amniotic fluid glucose and amino acid concentrations not only are consonant with those reported previously but also indicate that fetal fuel economy is directly related to the availability of maternal substrates. However, it becomes apparent that the siphoning effect of the fetoplacental unit must, by reason of the unit's small size, be less than that encountered in later gestation. Thus, the hypoglycemia associated with acute fasting in early pregnancy cannot be fully explained by the fetoplacental glucose requirements. It appears that differences in the fetal-maternal plasma glucose concentration reflect the metabolic requirements of the placenta.[27]

The magnitude of the hypoglycemia and hypoinsulinemia in three women who fasted in the second half

Table IX. Plasma glucose, insulin, and hGH levels after intravenous arginine in pregnant and nonpregnant women before and after a 72 hour fast

Duration of fast (hr.)	*Subjects*	*Minutes* 0	30	60	90
Glucose (mg./100 ml.)					
12	NP* (28)	86.1 ± 1.9†	107.1 ± 3.0	81.5 ± 3.3	75.2 ± 2.6
	P‡ (8)	66.7 ±2.2§	80.1 ± 2.9§	67.7 ± 3.6‖	64.3 ± 5.3
72	NP (18)	41.3 ± 1.7	44.2 ± 2.4	48.6 ± 1.7	54.3 ± 1.6
	P (12)	50.3 ± 2.2‖	51.7 ± 2.2¶	55.2 ± 3.1	60.9 ± 2.1#
Insulin (μU/ml.)					
12	NP (28)	17.4 ± 1.4	90.4 ± 8.6	38.2 ± 6.9	19.0 ± 2.0
	P (8)	5.6 ± 1.4§	36.6 ± 9.7	9.5 ± 2.2	3.7 ± 1.0
72	NP (18)	4.5 ± 0.9	5.4 ± 1.0	2.6 ± 0.7	2.9 ± 0.8
	P (12)	4.7 ± 1.1	7.4 ± 1.7	3.6 ± 1.1	3.3 ± 0.7
hGH (ng./ml.)					
12	NP (28)	3.4 ± 0.7	18.7 ± 3.6	27.8 ± 3.5	23.7 ± 3.4
	P (8)	4.3 ± 1.2	18.1 ± 4.4	26.3 ± 6.9	13.8 ± 2.7
72	NP (18)	2.2 ± 0.3	4.4 ± 0.9	12.3 ± 3.2	8.4 ± 2.1
	P (12)	1.3 ± 0.4	3.6 ± 0.9	12.9 ± 2.0	5.3 ± 1.0

*Nonpregnant.
†All values are means ± standard errors.
‡Pregnant.
§Value is significantly different from those in comparable nonpregnant subjects ($p < 0.001$).
‖Value is significantly different from those in comparable nonpregnant subjects ($p < 0.01$).
¶Value is significantly different from those in comparable nonpregnant subjects ($p < 0.05$).
#Value is significantly different from those in comparable nonpregnant subjects ($p < 0.02$).

of gestation was greater than anticipated. Since the size of the fetoplacental unit quadruples between the twelfth and twenty-eighth weeks of gestation, the hypoglycemia of late gestation is more related to the siphoning effect. The hypoaminoacidemia during fasting in late pregnancy was similar to that in earlier gestation, suggesting that maternal hepatic substrate utilization remains constant while the need for new glucose increases. Such deficits would lead to increased lipolysis.[28]

The net difference in the postabsorptive plasma glucose concentration between pregnant and nonpregnant women in early gestation may be related to an enhanced *maternal* substrate utilization under the influence of placental estrogen since this hormone influences carbohydrate metabolism in women of childbearing age as compared to men.[11, 29] Moreover, estrogen administration will lower the plasma glucose concentration in certain disease states associated with chemical diabetes.[30] Therefore, it is possible that the postabsorptive hypoglycemia in early gestation is related to the anti-insulin effects of estrogen as well as to a direct antagonism of the action of hGH at the periphery. Frantz and Rabkin[29] have reported enhanced ambulatory hypoglycemia in response to estrogen administration and, in response to this hypoglycemia, the ambulatory hGH secretion is in turn exaggerated.

In the first half of gestation, we have reported an augmented hGH response to the intravenous infusion of amino acids.[9, 13] In the present study, the hGH response to arginine in the first five minutes was greater in pregnant women although the maximal response in each group occurred simultaneously. That this increased responsiveness in pregnancy might be related to estrogen is suggested by the work of Fiedler and co-workers,[32] who, by pretreating women with clomiphene citrate, a known antiestrogen, demonstrated partial inhibition of hGH secretion in response to arginine.

The flux of gluconeogenic substrates to the liver from peripheral tissues doubles in the first 24 hours of fasting.[33] Hare and associates[3] reported that the failure to sustain euglycemia during fasting in pregnant rats was due to a restrained efflux of glucogenic amino acids from muscle in addition to fetoplacental parasitization of glucose. Felig and Wahren[6] have shown that the capacity for hepatic gluconeogenesis is augmented in fasting, even in the absence of pregnancy. In our studies, the increment in glucose and insulin following alanine infusion indicates hepatic integrity for amino acid utilization in terms of the over-all increase in the

plasma glucose concentration, and the hGH response to alanine at the height of the glycemic response confirms the specificity of alanine as a provocative stimulus of hGH secretion, at least during fasting. In that regard, hGH may modulate hepatic gluconeogenesis.

The insulin response in fasting women to alanine and arginine was expected since these are known to be insulin secretogogues.[34, 35] The diminished response could be related to the inadequate plasma glucose concentration[36]; however, Fink and co-workers[37] have shown that glucose-mediated insulin release is unaffected by prolonged starvation and the alteration and secretion may be related to the intracellular glucose concentration.[36, 38]

hGH release by arginine and alanine was marked in both groups of study patients. Moreover, the insulin-like effect of this pituitary polypeptide at the liver may be necessary during amino acid uptake.[28] In addition to the insulin and hGH responses to alanine, the glycemic response in pregnant women was less than that reported by Felig and associates[8] which may be due to the difference in the technique of administering the alanine.

As much as 1 Gm. of hPL is produced by the placenta in a 24 hour period. The production rate is dependent upon the functioning trophoblastic mass, showing the importance of placental size, and the synthesis and secretion of hPL are considered to be autonomous.[39, 40] The increase in hPL production in vitro is directly related to the availability of precursors,[41] but the effect of this increased production on maternal intermediary metabolism is still poorly understood.[40] Suwa and Friesen[41] evaluated ^{3}H-leucine incorporation into placental incubates and showed that a constant consumption of glucose was necessary for the production of hPL in addition to the iodinated precursors. After 96 hours, cellular degeneration was noted, and production decreased. Beck and Daughaday[40] reported impaired glucose tolerance but no lipolytic effect of hPL in 17 subjects receiving infusions for up to 12 hours. Ajabor and Yen[43] failed to observe a significant increment in hPL in response to induced maternal hypoglycemia, while others reported a short-lived (0.05 μg per milliliter) increase in hPL during induced hyperglycemia.[44] Spellacy and co-workers[39] have reported decrements in hPL in response to intravenous glucose. They have also shown increments in this placental polypeptide in response to insulin-induced hypoglycemia. Unfortunately, similar studies performed in this laboratory have not corroborated these data. Although hPL levels rose in response to prolonged fasting, we observed a gradual decrease in the magnitude of the response with advancing gestation. The possibility that elevated hPL concentrations merely represent the secretion of a prohormone cannot be excluded since the immunologic activity of hPL is not changed by any difference in molecular size.[45]

hPL reportedly influences in vitro protein synthesis,[46] and it may well be that hPL facilitates placental protein synthesis de novo by enhancing transamination especially under conditions of glucose deficiency. Increased hPL secretion in response to maternal fasting may be designed to accommodate increased amino acid production by the placenta in order to provide glucose precursors for fetal utilization. Placental size at each stage of gestation must be considered in the interpretation of the hPL concentrations. It is estimated that at three months' gestation placental weight averages 50 to 75 grams with a tripling in size to 225 grams by 24 weeks. This increased functioning placental mass is reflected in the increasing basal concentration of hPL. However, since increments in hPL in response to fasting decreased with advancing gestation, significant metabolic adjustments to starvation may have been made at the level of the placenta.

Fulfilling the role of a fetal liver in early gestation, the placenta may well respond to maternal starvation with gluconeogenesis or aminogenesis from nonglucose substrates, specifically, pyruvate and lactate.[29] Since gluconeogenesis within fetal tissues is limited prior to the twentieth week of gestation due to inadequate concentrations of glucose-6-phosphatase, placental glycogen may be utilized on either side of the intravillous space under the control of hPL. A placental metabolic role for hPL has been suggested by others.[41] The rise in hPL observed in a fasting woman carrying a dead fetus emphasizes this possibility.

The lipolytic effect of hPL reported by Grumbach and associates[47] has been challenged. Berle and colleagues[48] failed to observe a lipolytic effect in response to hPL injection, but unfortunately the dose used was so small that the possibility of demonstrable effect was reduced. The lipolytic effect of hPL may have been demonstrated in our study since a fourfold increase in the mean fatty acid concentration in pregnant women was observed. It should also be noted that such increments could merely have reflected hypoinsulinemia.

Except for the rapid depletion in maternal alanine concentrations, both the enhanced secretion of hPL and the marked ketonemia are difficult to explain. Permissible limits of neonatal hypoglycemia have been defined[49]; however, significant data with regard to the intrauterine fetus are lacking. The striking fetal

hypoglycemia observed in those fetuses delivered by hysterotomy from women who fasted served to raise speculation on the pathways of fetal cerebral metabolism in the presence of profound hypoglycemia. Fetomaternal hypoglycemia impairs the net uptake of amino acids by the fetal brain.[24] However, fetal glucose concentrations remained stable during prolonged maternal fasting in sheep even after fetal urea production has returned to normal.[26]

It is evident that voluntary starvation in early gestation has become an acceptable part of a planned weight reduction program for many women, and indeed such dietary restriction has been advocated in obesity.[50] While the present study permits few conclusions, we consider that a compromise in the fetal-placental fuel requirements brought about by maternal fasting may easily impair subsequent fetal development, and such impairments may not be evident for many years afterward.[51]

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Training in marital and sex counseling

Harold I. Lief, M.D., Professor of Psychiatry and Director of the Division of Family Study of the University of Pennsylvania School of Medicine (which incorporates the Marriage Council of Philadelphia and the Center for the Study of Sex Education in Medicine), announces a National Institute of Mental Health–sponsored training program for nonpsychiatric physician-educators and obstetrics/gynecology and family-practice residents. The program is designed to train physicians in marital and sex counseling and in teaching human sexuality to medical students and residents. The training period consists of full-time modules of five or nine months during the regular academic year or a part-time summer module of three months.

For faculty connected with medical schools who are either teaching or planning to teach human sexuality to medical students and to primary-care residents and who are able to attend the entire academic year, stipends of approximately $1,300 a month are available. For residents in obstetrics/gynecology or in other primary-care specialties, monthly stipends of approximately $1,000 a month are available.

For more details, interested applicants should contact: Ellen Berman, M.D., Director of Training, Assistant Professor of Psychiatry, Marriage Council of Philadelphia, 4025 Chestnut St., Second Floor, Philadelphia, Pennsylvania 19104.

Fluctuation of fetal hemoglobin in sickle-cell anemia

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A reduction of morbidity and mortality rates in homozygous sickle-cell patients was found in those with high fetal hemoglobin (Hb_F) levels. This factor would lead one to believe that an adequate amount of this substance would be protective to a patient with this hemoglobinopathy. This study utilizing pregnant and nongravid females, as well as males, followed for long periods of time indicates that the Hb_F level fluctuates with crisis. Some patients had low Hb_F levels with many crises and others had high amounts of Hb_F with no crisis. However, many patients with high levels on one occasion demonstrated a decrease in Hb_F levels when crisis occurred. More importantly, no patient had high levels of Hb_F during a crisis although the amount was elevated before and after the episodes. The possible explanation and ramifications of this finding are discussed.

NORMAL ADULT hemoglobin-A (Hb_A) contains four polypeptide chains, two alpha chains each comprised of 141 amino acids and two beta chains with 146 residues each. These polypeptide chains in combination with heme, a molecule of protoporphyrin and ferrous iron, form hemoglobin. Minor variations in the amino acid composition of the alpha and beta peptide chains can drastically alter the chemical and physical properties of the hemoglobin molecule. For instance, fetal hemoglobin (Hb_F) is comprised of two alpha chains and two gamma chains. The gamma chains differ from normal beta chains by the substitution of only two amino acids. It is this change in the polypeptide structures that ascribes to hemoglobin-F its alkali resistance[1] and its ability to absorb oxygen more readily than hemoglobin-A.[2] Normally Hb_F, which is abundant in the neonate, begins to decline at 3 to 4 months of age and decreases to the adult levels of less than 1 per cent during the fifth year of life. In some individuals, however, large amounts of Hb_F may persist due to certain hemoglobinopathies. These hematologic disorders include hereditary persistence of fetal hemoglobin (HPFH),[3] thalassemia,[4] and sickle-cell disease.[5] It appears that the percentage of Hb_F is usually constant for a given individual although it may be unequally distributed among the red cells themselves.

Although it is far from proved, there clinically appears to be a rough inverse correlation between the percentage of fetal hemoglobin and the severity of symptoms in sickle-cell disease. Individuals with sickle-cell anemia (HbS-S) possessing high levels of Hb_F appear to have fewer and milder crises.[5, 7] Conversely, it appears that those with frequent and severe hemolytic crises have low levels of Hb_F. In this report evidence is present that contradicts these beliefs and shows an indirect relationship between the level of Hb_F and the frequency of severe hemolytic crises in HbS-S patients. This association is exemplified by sickle-cell patients with high Hb_F levels that subsequently dropped during crisis only to rise after the crisis.

Materials and methods

The medical history of 36 adult female patients with hemoglobin S-S was reviewed. These patients had 56 gestations during the 5 year study period. All admissions and outpatient records were analyzed for hemolytic crisis, surgery, and medical complications as well as for pregnancy. Similarly the records of 12 nonpregnant females and 10 males with HbS-S were studied. The relationship of crisis to the amount of fetal hemoglobin was noted in each group.

Of the 56 pregnancies considered, all had been

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Table I. Association of fetal hemoglobin (Hb_F) with sickle-cell crisis during pregnancy

Pregnancies	*Hb_F% before pregnancy*	*Hb_F% during pregnancy**	*Hb_F% after pregnancy†*
I. With crisis during pregnancy (14)	5.5-16.5‡ 9.5§	0.0-1.0 0.8	0.0-15.0 6.5
II. No crisis during pregnancy (9)	4.5-17.0 10.0	5.0-15.5 9.5	5.0-16.5 9.5

*Taken during crisis or at term if no crisis present.
†2 to 4 months postpartum.
‡Range.
§Mean.

Table II. Relationship of fetal hemoglobin (Hb_F) to crisis in nonpregnant females and males

Patients	*Hb_F before crisis*	*Hb_F during crisis*	*Hb_F after crisis**
Group I. (10 males)	5.5-18.5† 10.5‡	0.0-1.5 0.6	3.0-10.5 5.5
Group II. (12 females)	4.5-16.5 9.5	0.0-1.0 0.5	0.0-12.2 6.5

*2 to 4 months.
†Range.
‡Mean.

evaluated prior to pregnancy relative to the percentage of Hb_F. Eight of this group did not have Hb_F determinations during their pregnancies and 4 died during hemolytic crisis and could not be further studied. These were eliminated from the study as well as an additional 21 patients who were lost to follow-up during that particular pregnancy or whose postpartum levels of Hb_F were not obtained. The remainder of the pregnancies (23), which were completely studied, are included in this investigation and are divided into two groups dependent on the occurrence of a crisis during the gestation. The average age, gravidity, and parity were approximately equal in both groups.

Qualitative examination of the various hemoglobins was carried out by starch block electrophoresis buffered to 8.6.[8] The percentage of hemoglobin-F was determined by alkali denaturation.[9] Special care was taken to exclude any patients who might have HPFA, thalassemia, hemoglobin S-Memphis, or other hematologic disorders in association with sickle-cell anemia.

Results

Table I shows the association of Hb_F with sickle-cell crisis in 23 patients who were included in this study. The patients were divided into two groups. Prior to their pregnancy, the first group of 14 patients (who did have a crisis during the gestation) exhibited a Hb_F ranging from 5.5 to 16.5 per cent with a mean of 9.5 per cent. However, in this group the percentage of Hb_F dropped precipitously to a mean of 0.8 per cent (range of 0.0 to 1.0 per cent) during crisis. The patients of Group I demonstrated a continual rise in the percentage of Hb_F during the postpartum period which ranged from 0.0 to 15.0 per cent with a mean of 6.5 per cent. These patients are compared to the 9 patients in Group II who had a similar antepartum range of Hb_F (4.5 to 17.0 per cent) with a mean of 10.0 per cent. These patients had no crises and showed similar pregnancy Hb_F levels with a mean of 9.5 per cent. Similarly these patients maintained approximately the same level of Hb_F at the postpartum visit (range 5.0 to 16.5 per cent) with a mean of 9.5 per cent.

The relationship of Hb_F to crisis in nonpregnant females and in males is shown in Table II. Group I represents a study of 10 males with sickle-cell disease and Group II is comprised of 12 nonpregnant female patients. As indicated by the data, both groups of patients display similar patterns concerning Hb_F levels before, during, and after crisis. Both groups showed a marked reduction of Hb_F during sickle-cell crisis (means of 0.6 and 0.5 per cent, respectively). This is in agreement with the levels found in the pregnant females who underwent crisis during gestation (see Table I). The data of Table II also signifies that a slow return to normal levels of Hb_F is observed in both groups over a 2 to 4 month period.

Comment

Chernoff[10] reported that up to 80 per cent of patients with sickle-cell anemia have elevated levels of Hb_F that range from 4 to 16 per cent. In this study similar elevations in Hb_F were found in males as well as pregnant and nonpregnant females. It has been suggested that sickle-cell anemia patients with higher percentage of Hb_F have fewer and less severe crises than those patients who have low levels of this hemoglobin.[5, 7] The pregnant patients in Group II of Table I seem to confirm the supposition that patients with high levels of Hb_F are not as likely to have crisis. Indeed, one of the women studied had 12 pregnancies with no crisis during pregnancy and no change in her Hb_F percentage. Furthermore, many of these women were studied over a period of several years and their Hb_F levels remained essentially constant. In addition, they did not show a tendency toward sickle cell crisis in the nonpregnant state. Similarly, it was found in this investigation that most patients with sickle-cell anemia and a low Hb_F tend to have more frequent and severe crises. For instance, of the patients eliminated from the

study, 2 of the women who died in sickle-cell crisis during pregnancy and 2 additional gravid women who were lost to follow-up had extremely low levels (average 0.5 per cent) of Hb_F on multiple examinations. These 4 patients were subject to multiple crises and, as confirmed by the two maternal deaths, the crises tended to be much more severe. These data tend to support the premise that sickle-cell anemia patients with high levels of Hb_F are "protected" while those with low or nonexistent levels of Hb_F are susceptible to crisis.

However, the remainder of the data would suggest a different hypothesis, namely that the Hb_F level fluctuates downward during crisis and is high in the absence of a crisis. For instance, it would appear from those patients in Group I of Table I that the Hb_F, although high antepartum, decreases during a crisis and then increases postpartum. This would indicate that, at least in some HbS-S patients, the high level of Hb_F is not "protective" during pregnancy and varies with the occurrence of a crisis. Further evidence is seen in the other two maternal deaths and nine members of the original group lost to follow-up who had high Hb_F levels prior to crisis only to have them decrease during crisis. Some might argue that it is the effect of the gestation which causes the fluctuation in Hb_F rather than the crisis. However, both the nonpregnant females and male HbS-S patients in Table II refute this as they show decreases in Hb_F associated with crisis. This appears to emphasize the lack of correlation of this phenomena with pregnancy or gender. Indeed, there were no patients in our study, including these incompletely studied, who had a high level of Hb_F during crisis. Therefore, it appears that the reduction of Hb_F during crisis is a reproducible phenomenon related to the crisis.

It is interesting also to note that 4 of the 9 women who did not have a crisis with pregnancy (Group II, Table I) are included in the group of 12 nonpregnant females (Group II, Table II). These same women who were "protected" by the high Hb_F levels during gestation experienced crisis with a drop in Hb_F values later in the nonpregnant state. For instance, 1 of these 4 patients experienced frequent crisis and low Hb_F as a child but the level of Hb_F increased as the patient matured and the sickle-cell crises ceased. The patient had two pregnancies with no difficulty. However, 2 years later in the nongravid state she began to have crises that were associated with low Hb_F levels.

From the data presented, the trend toward a reduction of fetal hemoglobin just prior or during crisis appears to take place in all patients. However, one would expect the Hb_F-containing cells to survive longer because of their greater oxygen-carrying capacity.[5] Possible explanations for this paradox are as follows: (1) the Hb_F-containing cells are slightly larger than the sickle cells and may become trapped more rapidly during "plugging" of the microcirculation in crisis; and (2) if more fetal hemoglobin is carried by a particular red blood cell, the electric charge may be changed and consequently it may be more susceptible to sickling. In addition, there is no explanation for the increased incidence of crisis and earlier death which is prevalent in patients with low Hb_F. However, this study demonstrates that many patients with high Hb_F will experience crisis if they were followed long enough. This difference may be on a genetic basis since it has been shown by Schroeder and associates[11] and Huisman and associates[12] that Hb_F contains at least two types of gamma chains and that these are products of nonallelic genes. In addition, there may be molecular differences related to other chains in the hemoglobin molecule or to the heme molecule itself which have not been previously detected. These differences might explain one individual having "protection" while another does not. This concept is supported, at least in part, by the finding of some rather benign S-containing hemoglobins such as hemoglobin S-Memphis. Therefore, on the basis of genetic difference alone, it may be possible that the F and S hemoglobin may be slightly altered to change the clinical behavior of patients possessing those genes. Most of these changes, of course, are not detectable by current methods.

Although a gravid HbS-S patient with a high Hb_F may not be expected to experience crisis, one cannot assume that the elevated Hb_F will "protect" her during parturition, because it appears the Hb_F level is subject to change. Also, other factors may influence the condition of the patient. This point is exemplified by the data of this report. In these 56 pregnancies there were four deaths. All of these occurred during labor and delivery and two of the four occurred in patients with high antepartum levels of Hb_F. Therefore, since the mortality and morbidity rate appears to be increased in pregnant patients with HbS-S, one should consider aggressive therapeutic modalities, such as partial exchange transfusion during gestation.[13, 14] Following delivery, education of the patient, detection of disease in family members, prevention of crisis, and family planning should be emphasized.[15]

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Initiation of human parturition

IV. Demonstration of phospholipase A_2 in the lysosomes of human fetal membranes

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In this study we sought to define the subcellular localization of phospholipase A_2 in human fetal membranes. Others have postulated a role for decidual lysosomes in the initiation of human parturition.[5] We hypothesized that if phospholipase A_2 were localized within lysosomes of fetal membranes the accelerated expression of the activity of this enzyme could be prevented until such time as the metabolic events of parturition begin. At parturition a perturbation of the lysosomal membrane within the chorio-amnion could result in an increased release of free arachidonic acid through an accelerated activity of phospholipase A_2. The results of this study suggest that at least a portion of phospholipase A_2 in the chorion laeve and amnion is localized in the lysosomal fraction.

A CONSIDERABLE BODY of evidence has accrued to support the concept that human parturition is initiated by the action of the prostaglandins E_2 and/or $F_{2\alpha}$ on the myometrium. Moreover, the prostaglandin synthetase enzyme complex has been demonstrated in uterine decidua.[1] The enzymatic release of arachidonic acid from glycerophospholipids is considered to be of crucial importance in the control of the regulation of prostaglandin synthesis. This obtains since only free arachidonic acid can serve as the precursor of prostaglandins E_2 and $F_{2\alpha}$, and fatty acids are ordinarily present in an esterified form in tissues.

The polyunsaturated fatty acids, e.g., arachidonic acid, are primarily esterified in the 2 position of glycerophospholipids. Therefore, the action of the enzyme that catalyzes the release of fatty acids from the 2 position of glycerophospholipids, phospholipase A_2, is of signal importance in the control of the rate of biosynthesis of prostaglandins E_2 and/or $F_{2\alpha}$. The fetal membranes of both laboring and non-laboring women contain significant amounts of esterified arachidonic acid[2] and the activity of the enzyme phospholipase A_2.[3] A critical question relating to the onset of human parturition revolves about the mechanism of expression of the activity of phospholipase A_2.

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Materials and methods

Following vaginal delivery of normal gravidas, placentas with attached fetal membranes were immediately placed in a chilled solution of 0.25M sucrose and the container was immersed in ice. Fetal membranes were rapidly removed from the placenta and immediately transferred to 0.25M sucrose. A segment of the membranes was placed fetal side down in a shallow tray containing cold sucrose and the decidua was dissected from the chorion laeve with forceps. The membranes were washed three times with cold sucrose, blotted, and weighed.

Samples of chorio-amnion were homogenized in 0.25M sucrose (1:3, weight per volume) with the

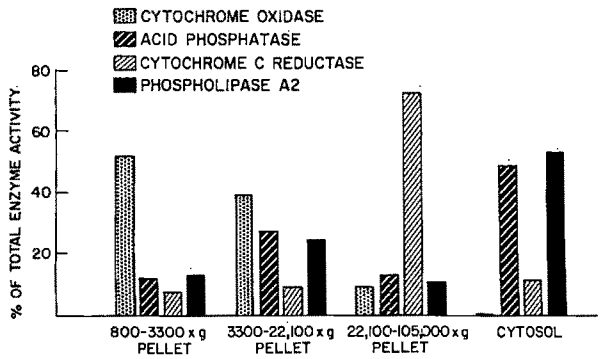


Fig. 1. Distribution of cytochrome oxidase, acid phosphatase, NADPH-dependent cytochrome c reductase, and phospholipase A_2 in subcellular fractions of human chorioamnion. The activities depicted are the means of four separate sets of chorioamnion obtained from women delivered at term.

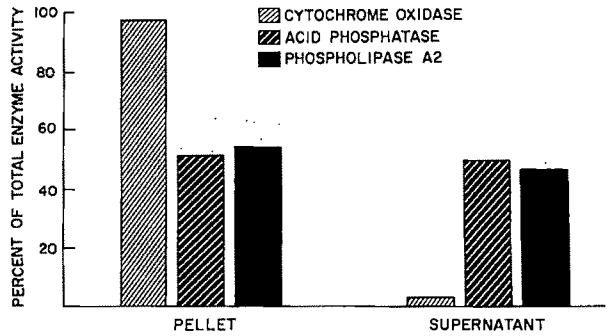


Fig. 2. Distribution of cytochrome oxidase, acid phosphatase, and phospholipase A_2 after homogenization of an 800 to 22,100 × g pellet and subsequent recentrifugation.

Polytron at its slowest speed employing the small probe for one minute, then in a Dounce homogenizer using ten strokes of the loose-fitting pestle, and thirty strokes of the medium-fitting pestle. Subcellular fractions were prepared from whole homogenates by centrifuging at 800 × g for 10 minutes, followed by successive centrifugation of the resulting supernatant fractions at 3,300 × g for 10 minutes, 22,100 × g for 30 minutes, and 105,000 × g for 60 minutes.

Each pellet was resuspended in 0.25M sucrose. The activities of cytochrome oxidase [EC 1.9.3.1 (a mitochondrial marker enzyme)], NADPH-dependent cytochrome c reductase [EC 1.6.2.3 (a microsomal marker enzyme)], and three lysosomal marker enzymes, acid phosphatase (EC 3.1.3.2), β-glucuronidase (EC 3.2.2.31), and cathepsin B_2 were measured. The activity of phospholipase A_2 (EC 3.1.1.4) was assayed according to the procedure previously described.[3] The activities of each marker enzyme and of phospholipase A_2 were measured in each pellet and in the final supernatant fraction (cytosol).

In a second series of experiments the pellets obtained at 3,300 × g and 22,100 × g were combined and rehomogenized in 0.25M sucrose using a Potter-Elvehjem homogenizer. This homogenate was resedimentated by centrifugation at 105,000 × g for 60 minutes and the activities of cytochrome oxidase, acid phosphatase, and phospholipase A_2 were measured in the pellet and supernatant fraction.

Results

The activities of three lysosomal enzymes, β-glucuronidase, cathepsin B_2, and acid phosphatase were assayed in each subcellular fraction as illustrated in Table I. The per cent of the total activity in the various subcellular fractions was similar for each of the three lysosomal marker enzymes. Therefore, the activity of acid phosphatase is used to illustrate the distribution of all three lysosomal marker enzymes in the figures. The distribution of cytochrome oxidase, acid phosphatase, NADPH-dependent cytochrome c reductase, and phospholipase A_2 observed in subcellular fractions of human fetal membranes is graphically depicted in Fig. 1. The results of this study permit the following conclusions. (1) Phospholipase A_2 activity paralleled the activity of acid phosphatase in each subcellular fraction, suggesting a lysosomal distribution of phospholipase A_2. (2) The activities of the lysosomal marker enzymes are greatest in (a) the 3,300-22,100 × g pellet, likely representing intact lysosomes, and in (b) the cytosol, probably representing enzyme activity from disrupted lysosomes. (3) The activity of the microsomal marker enzyme is principally confined to the 22,100 to 105,000 × g pellet which contains little phospholipase A_2 activity, suggesting that little if any phospholipase A_2 is associated with microsomes. (4) There is a considerable portion of the activity of the mitochrondrial marker enzyme in the 3,300 to 22,100 × g pellet suggesting that both mitochondria and lysosomes are present in this pellet.

Since phospholipase A_2 in other mammalian tissues has been reported to be present in both mitochondria and lysosomes, a second series of experiments was performed to differentiate between these two possible subcellular locations of phospholipase A_2 in fetal membranes.

The distribution of cytochrome oxidase, acid phosphatase, and phospholipase A_2 was measured in the pellet and supernatant fraction following the homogenization and recentrifugation of a combined

Table I. Distribution of three lysosomal marker enzymes in subcellular fractions of human fetal membranes

	Per cent of total activity		
	Acid phosphatase	*β-glucuronidase*	*Cathepsin B_2*
800-3300 × g pellet	11.5	12.0	13.5
3300-22,100 × g pellet	28.0	29.0	33.5
22,100-105,000 × g pellet	12.0	16.5	6.5
Cytosol	49.5	43.0	46.0

subcellular fraction enriched in both lysosomes and mitochondria. This homogenization was designed to further disrupt lysosomes. The results of this study are graphically illustrated in Fig. 2. It is evident that this homogenization resulted in a parallel release of the activities of phospholipase A_2 (46 per cent) and of the lysosomal marker enzyme, acid phosphatase (49 per cent), into the supernatant fraction. In contrast, the mitochondrial marker enzyme activity could not be definitely demonstrated in the supernatant fraction but rather was quantitatively recovered in the pellet (>95 per cent). The solubilization of significant quantities of phospholipase A_2 and acid phosphatase activities from the 800-22, 100 × g pellet into the supernatant fraction under conditions known to disrupt lysosomes, provide further evidence for a lysosomal distribution of phospholipase A_2 in human fetal membranes.

Comment

We have previously reported that free arachidonic acid content of amniotic fluid is disproportionately increased in laboring women when compared to that from women not in labor; and that the instillation of arachidonic acid into the amnionic sac results in abortion in midpregnancy and in parturition in women with a dead fetus in late pregnancy.[6] Furthermore, we have demonstrated that phospholipase A_2 is present in the human chorioamnion and that arachidonic acid represents nearly 20 per cent of the total fatty acid content of human chorio-amnion. Since arachidonic acid is found primarily in the 2 position of glycerophospholipids, the release of free arachidonic acid, the obligatory precursor of prostaglandins E_2 and $F_{2\alpha}$ must be catalyzed by phospholipase A_2.

The results of the present study suggest that phosopholipase A_2 is present in the lysosomes of human fetal membranes. This observation has considerable potential in defining the metabolic events that lead to parturition. The phospholipase A_2 may be present in lysosomes throughout the course of gestation, but an accelerated expression of the enzyme activity may occur only after the perturbation of the lysosomal membrane allows an increased interaction between substrate and enzyme. Within the framework of this concept certain previously enigmatic clinical events resulting in premature labor could be explained. Certain factors are known to perturb lysosomes; such as trauma or abrupt changes in osmolality, as in intra-amnionic injection of hypertonic solutions or premature rupture of fetal membranes; changes in tissue pH, as may occur in inflammation and/or infection of the fetal membranes; and anoxia, as may occur with separation of the membranes from the underlying uterine decidua.

In the course of normal parturition, a self-perpetuating sequence of cascading metabolic reactions could eventuate from the initial accelerated expression of phospholipase A_2 activity since both lysophospholipids and the prostaglandins synthesized from the released arachidonic acid are known to be capable of altering lysosomal membranes.

Summary

The subcellular distribution of human chorioamnion phospholipase A_2 has been examined. That at least a portion of phospholipase A_2 is lysosomal in human choriamnion has been suggested by assay of marker enzyme activities in subcellular fractions prepared by differential centrifugation and by solubization of phospholipase A_2 under conditions known to disrupt lysosomes. The importance of the lysosomal localization of the enzyme activity and its relationship to the regulation of arachidonic acid release, prostaglandin formation, and the initiation of human labor is presented.

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Actions of the uterine relaxant, fenoterol, on uteroplacental hemodynamics in human subjects

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The action of fenoterol, a uterine relaxant of the adrenergic β-mimetic group of drugs, has been investigated on placental, myometrial, and cardiac blood pools. ^{113m}Indium was injected intravenously and the blood pools were measured by recording γ activity externally. In eight cases with oxytocin-induced labor, fenoterol inhibited the typical blood pool changes of labor, i.e., contraction-synchronized decrease of placental and myometrial blood pools with increase in cardiac blood pool. Furthermore, fenoterol produced an increase in placental and myometrial pools with corresponding decrease of cardiac blood pool. These changes were observed consistently. In four other cases, of which three had spontaneous labor, similar effects were observed. The possible mechanisms of hemodynamic action of fenoterol, with reference to uterine relaxation, are discussed.

THE USE of uterine relaxants in obstetrics has aroused increasing interest in recent years, especially the adrenergic β-mimetic group of drugs.

While the action of β-mimetic drugs in inhibiting uterine muscle activity was established early, a dose large enough to induce uterine relaxation also produced intolerable side effects on the heart and circulation, so prohibiting their clinical use. Thus, a preparation with a more selective action was sought. Theoretically, the receptor system for β-mimetic actions has been subdivided by Lands and associates,[1] β_1 receptors being responsible for cardiac and metabolic actions and β_2 receptors for actions on smooth muscle organs, e.g., bronchus, blood vessels, and uterus. The uterine relaxants now in use possess predominantly β_2-stimulating activity but some β_1 activity is still present, leading to undesirable side effects. In high doses they may lower the blood pressure and increase the pulse rate, and subjective sensations such as internal restlessness, heart throbbing, drowsiness, sickness, and hand tremor have been reported.[2] A new β-mimetic drug with a favorable $\beta_2:\beta_1$ ratio is the drug fenoterol, which was originally developed for selective bronchospasmolysis. It is an orciprenaline derivative with the structure shown in Fig. 1.

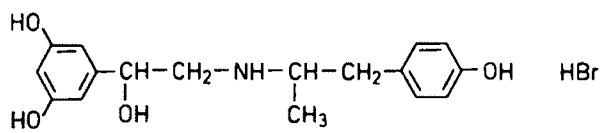


Fig. 1. Structural formula of fenoterol.

After discovery of its effective uterine relaxant action, its use in obstetrics has spread quickly. It seems superior in action compared to other uterine relaxants belonging to the β-mimetic group.[3] Since β mimetics generally increase circulation in skeletal muscle,[4] it was of interest to investigate the influence of fenoterol on uteroplacental hemodynamics in human beings.

Method

The actions of fenoterol were investigated in 11 patients (12 examinations) who had been admitted to hospital in the third trimester of pregnancy because of various pregnancy complications. The hemodynamic evaluation consisted of continuous recording of uteroplacental blood volume as described.[5] In brief, the method consists of injecting 0.5 mCi of ^{113m}In into the cubital vein and continuously measuring the γ activity over the heart, placenta, and placenta-free myometrium. After uniform distribution of the tracer in the

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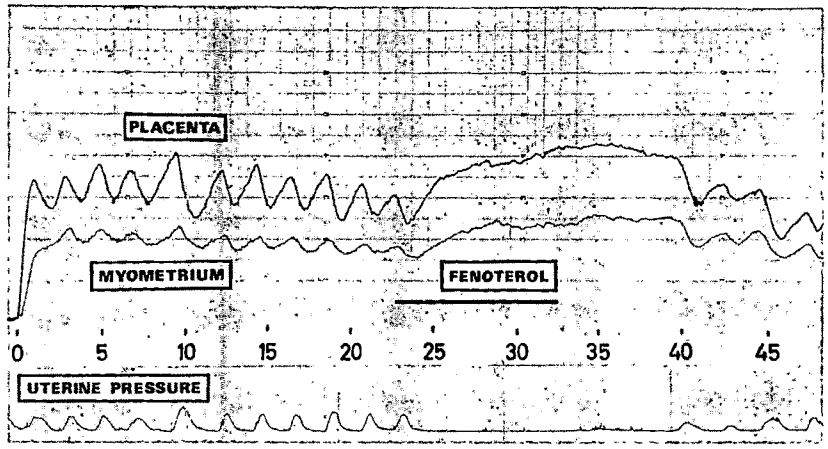


Fig. 2. Above: Placental and myometrial blood pool tracings in a 33-year-old woman, para 2, in the thirty-sixth week of pregnancy. The abscissa shows time in minutes and the ordinate measures γ activity in counts per minute. Below: Uterine pressure measured by external tocography.

Table I. Changes in cardiac, placental, and myometrial blood pools following administration of fenoterol in 12 cases. Results, the averages of 10 minute measurements, are expressed as percentages of the pretreatment values

Case No.	*Heart*	*Placenta*	*Myometrium*
1	−37	+37	+129
2	−19	+20	+34
3	−3	+16	+22
4	0	+70	+8
5	—	+66	+39
6	−15	+29	+38
7	−7	+46	+49
8	−22	+83	+40
9	−10	+64	+39
10	−3	+11	—
11	−12	+28	+15
12	−10	+17	+50
$\bar{x}$	−12.5	+40.5	+42.1

intravascular space, variations of the registered γ activity reflected blood pool changes.

In the present work, medicament-induced blood pool changes were evaluated quantitatively, as follows. A 10 minute section of curve immediately prior to the drug injection was compared with an equal length of the curve after drug administration. Twenty impulse integrals of one-half minute duration for each section were then corrected according to ^{113m}In decay ($T\frac{1}{2}$ = 1.66 hours). Then, the average of the values in the pretreatment phase was taken as 100 per cent and changes in the curve section after drug administration were expressed as percentages of this value. Statistical calculations of the results were done with the non-parametrical tests (Wilcoxon signed-rank test and Mann-Whitney U test). A normal distribution could not be expected since the patients were admitted with varying degrees of pathologic conditions. As an aid in the diagnosis of placental insufficiency due to disturbed hemodynamics, the initial part of the γ activity tracings was evaluated as described.[5]

In eight cases an oxytocin stress test according to Hammacher[6] was performed to reveal a latent placental insufficiency and also to show the effect of fenoterol on labor activity. Fetal heart frequency and labor were monitored with a cardiotocograph (Hewlett Packard). The patient lay in the supine position, tilted about 15° toward one side, for one-half hour before and during the investigation.

The fenoterol injection was administered 15 to 20 minutes after the ^{113m}In injection. Fenoterol (0.06 mg. in 7.5 ml. of saline) was injected intravenously in 5 to 12 minutes according to the side effects observed. The action of fenoterol was observed for 20 to 30 minutes and in all cases with induced labor the oxytocin infusion was continued during this time.

Results

Fig. 2 shows typical γ activity tracings from placenta and myometrium in a 33 year old woman, para 2, gravida 3, in the thirty-sixth week of pregnancy (Case 7). The ordinate measures γ activity in counts per minute, the abscissa the time in minutes. The lowest tracing records uterine pressure measured by external tocography. The first half of this tracing shows regular oxytocin-induced contractions and these are reflected simultaneously in the upper two tracings as blood pool changes. Since the recording apparatus had two channels, blood pool changes in only two organs, e.g., placenta and myometrium, could be recorded on one

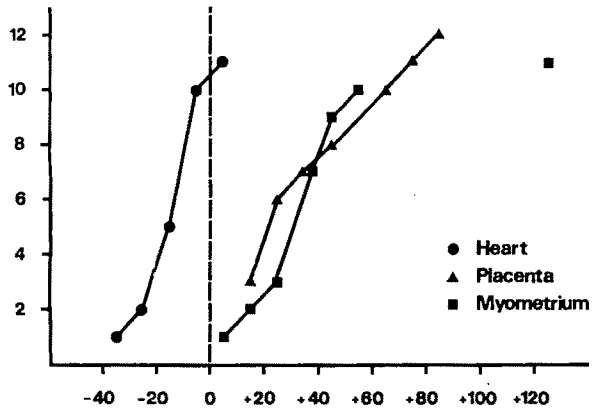


Fig. 3. Cumulative graphs of blood pool changes following administration of fenoterol. The abscissa shows the deviations from pretreatment values in percentages, the single values grouped together at 10 per cent intervals. The ordinate gives the number of patients.

Table II. Changes in placental and myometrial blood pools following fenoterol in the cases with regular pretreatment contractions. The results are averages of 10 minute measurements expressed as percentages of the mean peak counting rates obtained between pretreatment contractions

Case No.	*Placenta*	*Myometrium*
1	+29	+91
2	+14	+24
3	+11	+14
4	+59	−2
6	+21	+31
7	+30	+40
8	+63	+37
10	+4	—
12	+7	+19
$\bar{x}$	+26.4	+31.7

tracing. Blood pool changes in the heart were registered simultaneously and later recorded. These changes corresponded with those of placenta and myometrium but in inverted form, i.e., when the blood pool in the placenta increased, there was a decrease in heart blood pool, and vice versa.

After the fenoterol injection, the contractions were inhibited, the placental and myometrial blood pools increased, while the heart blood pool decreased. These changes are shown directly without decay correction or mathematical evaluation.

In Table I, the blood pool changes which occurred following the dose of 0.06 mg. of fenoterol are summarized for all cases. No oxytocin stress test was performed in Cases 5, 8, 11, and 12. In one patient, duplicate measurements were made (Cases 5 and 6). The results given in Table I are the average values of the 10 minute curve sections immediately after the injection was completed, expressed as percentages of the 10 minute preinjection curve section. Statistical calculations were performed to establish whether the fenoterol action differed in oxytocin-treated and -untreated patients. Since no significant differences were found with the Mann-Whitney U test, further calculations were done on all patients as a single group. After fenoterol, the blood pool of the heart decreased 12.5 per cent while the placental and myometrial blood pools showed increases of 40.5 and 42.1 per cent, respectively. In a comparison of pre- and postmedication phases, the Wilcoxon signed-rank test showed significant differences in all three blood pool changes, with the 2p value in each case being less than 0.005.

In Fig. 3, the distribution pattern of the blood pool changes can be seen as cumulative graphs of the single values. The heart curve is moved to the left and covers a variation compass of 40 per cent, showing in its form, normal distribution of the single values. As a complementary action, the placental curve is moved to the right with a variation compass of 70 per cent and the form of the curve does not show the typical "S" shape. The myometrial curve, however, is, with the exception of one extreme value of +130 per cent, similar in shape to the heart curve showing a normal S-form distribution.

Since the blood pools in placenta and myometrium decrease during uterine contractions and this effect was not taken into account in the previous calculations, it is possible that the blood pool changes observed following fenoterol could have been due to cessation of contractions alone. Thus, in the patient group in which regular contractions were recorded (9 cases), the average peak counting rate obtained between contractions was compared with that achieved during the period of drug-induced uterine asystole. Table II shows these blood pool increases following fenoterol with the average 10 minute measurements now expressed as percentages of the mean peak counting rates obtained in the predrug period.

While the uterine contractions have obviously affected the degree of blood pool changes, the results demonstrate that in the cases studied (with one exception, Case 4, myometrium) substantial increases in placental and myometrial blood pool size occurred. The average increase for placenta was 26.4 per cent and for myometrium 31.7 per cent. The Wilcoxon signed-rank test showed that these differences were significant, with the 2p value for placenta less than 0.01

Table III. Actions of fenoterol on labor activity

Case No.	*No. of contractions in the 10 minute phase before fenoterol*	*Induction of labor with oxytocin infusions*	*Duration of fenoterol injection (min.)*	*Duration of uterine relaxant action (min.)*
1	4	5.00 m.U./min.	6	26
2	5	6.25 m.U./min.	6	20
3	4	3.75 m.U./min.	5	28
4	4	5.00 m.U./min.	8	>37
5	0	0	12	—
6	4	6.25 m.U./min.	11	>36
7	5	3.75 m.U./min.	10	16
8	4	0	11	>37
9	Contracture of 6 min.	8.75 m.U./min.	8	16
10	4	3.75 m.U./min.	10	25
11	1	0	8	29
12	3	0	8	>32

Table IV. Results of hemodynamic measurements in patients treated with fenoterol related to complications of pregnancy and outcome of pregnancy

				Hemodynamic values		*Outcome of pregnancy*		
Case No.	*Age*	*Parity*	*Pregnancy complication and week of pregnancy*	*Placental build-up time (min.)*	*Placental pool changes after fenoterol (%)*	*Birth weight (Gm.)*	*Gestation age (wk.)*	*Percentile*
1	29	0	Pre-eclampsia (mild) 42	1.7	+37	3,710	43	50-75
2	27	2	Pathol. FHR 42	2.3	+20	3,730	43	50-75
3	28	2	Pre-eclampsia (mild) 39	1.7	+16	3,220	40	25-50
4	27	0	Oligohydramnios 40	1.9	+70	2,750	41	5-10
5	35	1	Pre-eclampsia (mild) 36	3.0	+66	2,050	39	<5
6	35	1	Pre-eclampsia (severe) 38	5.6	+29	2,050	39	<5
7	33	2	Thalassemia 36	1.0	+46	3,270	40	25-50
8	38	1	Pre-eclampsia (mild) 28	1.6	+83	3,070	40	10-25
9	28	0	Pre-eclampsia (mild) 39	3.0	+64	3,140	40	25-50
10	24	1	Suspected growth retardation 38	1.7	+11	3,080	39	25-50
11	33	1	Pre-eclampsia (mild) 38	2.7	+28	3,300	40	25-50
12	29	0	Pre-eclampsia (mild) 36	2.3	+17	2,960	40	10-25

and for myometrium less than 0.05. Thus, with the vascular effect of the uterine contractions taken into account, the capacity of the uteroplacental vascular bed has clearly been increased by the uterine relaxant, fenoterol.

The effects of fenoterol on labor activity are summarized in Table III. For the oxytocin stress test (eight cases), oxytocin infusions of 3.75 to 8.75 m.U. were given and labor frequencies of 4 to 5 contractions per 10 min. were elicited. Case 9 is an exception, with a contracture of 6 minutes.

In all eight oxytocin cases given fenoterol, complete suppression of labor activity was observed in spite of continuation of the oxytocin infusion. The duration of labor suppression varied from 16 minutes to more than 37 minutes, the latter being the longest observation time.

In the four cases without oxytocin, two had relatively

strong labor which was suppressed by fenoterol throughout the observation periods of 32 and 37 minutes.

The maternal heart frequencies increased in 11 out of 12 cases, up to a maximum of 140 beats per minute. Fetal tachycardia was observed in five out of 11 cases.

Table IV shows the placental pool changes following fenoterol related to pregnancy complications at the time of investigation, the outcome of pregnancy, and the placental buildup time values. As previous work has indicated,[7] a placental buildup time of more than 3 minutes indicates the presence of a pathologic condition. In the present collection, this occurred only once. This patient had duplicate measurements made in the thirty-sixth (Case 5) and thirty-eighth (Case 6) weeks of pregnancy. Pre-eclampsia developed during this period from mild to severe. The build-up time increased from 3.0 to 5.6 minutes while the increased placental blood pool induced by fenoterol decreased from 66 to 29 per cent. This was the only patient in the series for whom the oxytocin stress test gave a pathologic result with late decelerations in FHR patterns after the oxytocin-induced labor. At birth, the baby was small-for-date with a percentile of <5. It should also be noted that the greatest placental pool increase occurred in the twenty-eighth week (Case 8), i.e., the earliest stage of pregnancy in the group examined. In cases with small placental pool increases, i.e., under 20 per cent, no connections with pregnancy complications were observed.

Comment

In the present investigation, fenoterol increased the uteroplacental blood pools in both the placenta and the myometrium.

Two possible modes of action are suggested. First, fenoterol could cause vasodilatation by a direct action on the uteroplacental blood vessels. In human subjects, the innervation of these vessels has not yet been demonstrated. In the pregnant uterus, the current information has been derived almost exclusively from animal experiments. Duncan and Lewis[8] showed that in rabbits, in hypoxic conditions, the placental and myometrial circulations were affected differently. In 1972, Greiss[9] found that in sheep the blood vessels of the myometrium reacted well to α- and β-adrenergic drugs whereas the placental vessels were largely insensitive to these stimuli. The results reported here show that in the human being the β-mimetic fenoterol induced blood pool increases not only in the myometrium but also in the placenta. These pool changes result from an increased capacity of the uteroplacental vascular bed and are not entirely due to cessation of uterine contractions, as demonstrated in Table II.

There was no correlation apparent between percentage increase in myometrial and placental blood pools; in fact, in some cases myometrial increase was greater, whereas in others the placental pool showed a larger increase. From this, it seems likely that the enlarged placental blood pool represents an actual augmentation of the volume of blood in the intervillous space. This would imply either a dilatation of the spiral arteries or an increased venous resistance to drainage of blood from the intervillous space. The latter of these possibilities, however, seems much less likely than the former. Thus, the data suggest that in contrast to the observation of Greiss in sheep, the uteroplacental arteries in the human are sensitive to β-sympathomimetic stimuli, according to Lands and associates,[1] by stimulation of β_2 receptors.

A second possible explanation for increase in uteroplacental blood pool by fenoterol is by an indirect action, following increased maternal cardiac output. As has been shown in animal experiments, the pregnant uterus has no autoregulatory mechanism[10, 11] and is not able to produce reactive hyperemia.[12] Although the pregnant uterus reacts to maternal stress situations such as hypoxia[12, 13] and circulatory shock[14] by vasoconstriction and reduced blood circulation, normally, uterine blood flow is directly related to maternal cardiac output.[10, 11] As a β-mimetic drug, fenoterol increases cardiac output[15] by its action on the β_1 receptors. Such an indirect effect is supported by the results of the present work, which showed a consistent decrease in cardiac blood pool. As Sjöstrand[16] has described, an increase in cardiac output results in depletion of the blood store in the thoracic region. Therefore the observed decrease in blood pool may have been due to a decrease in the precardial blood pool. The main factor contributing to increased cardiac minute volume is maternal tachycardia which occurred in 11 out of 12 cases.

With the technique described, only the increases in blood pool of placenta and myometrium due to fenoterol could be recorded. In all probability there was an accompanying increase in circulation, this assumption being supported by results of animal experiments. Klöck and associates[17] showed in sheep of advanced pregnancy, that after administration of β-adrenergic uterine relaxants, fenoterol among them, there was an increase in uterine circulation. In human patients, with isoxsuprine, a β-adrenergic uterine relaxant, an increase in uterine circulation has also been observed.[18] With the aid of the thermistor needle

method, circulation in the cervix was measured but these results are restricted to the cervix.

In the present work, a further indirect indication for an increase in blood flow produced by β-mimetic drugs was obtained by making the following observations. In 3 patients, a second injection of ^{113m}In was given after the development of blood pool increases in placenta and myometrium induced by fenoterol. In all three cases, the second buildup time was shorter than the first. This was interpreted as an indication of increased blood flow.

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Ultrastructural observations of the human uterine smooth muscle cells during gestation

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At term pregnancy, the myometrium consists of bundles of smooth muscle cells bound together by varying amounts of connective tissue. Each bundle contains both dark and light muscle cells. During uterine contractions it is believed that the smooth muscle cells become darker, decrease in volume, and exhibit changes in diameter. This is accompanied by widening of the interspaces and by a decrease in the areas of cellular contact. Between contractions, there are more light cells which become arranged closer to each other and exhibit large areas of interdigitation. The significance of these observations in the mechanism of uterine contraction and retraction is discussed. Cells believed to be modified smooth muscle cells occupy the myoendometrial junction and the decidua basalis. They are irregular in shape, poor in myofilament content, and rich in other cytoplasmic organelles and form a loosely arranged layer of cells between the myometrium and the trophoblast. The possible functional significance of these cells is also discussed.

HUMAN UTERINE smooth muscles exhibit several changes in morphology during pregnancy. I[1, 2] reported on changes in the myometrial muscle cells of the guinea pig at term pregnancy and their possible physiologic significance. Dark and light smooth muscle cells have been described, and the changes that accompany contraction of isolated strips of uterine smooth muscle cells in vitro were reported by Gansler.[3] Based on morphologic observations of the contracting uterine muscle in vivo made in this study at the electron microscopic level, an attempt will be made to explain the mechanisms of uterine contraction and retraction during labor and delivery.

In the nongravid uterus, a sharply defined irregular line of demarcation exists between the noncontractile endometrium and the contractile myometrium; and the two tissues are joined together by connective tissue. As pregnancy continues, a new layer of specialized cells, observed in this study, occupies the myoendometrial junction and the basal decidua. An attempt to explain the physiologic significance of this layer of cells as a buffer zone between the contracting myometrium and the noncontractile decidua of pregnancy constitutes another part of this study.

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Material and methods

Myometrial and adjacent endometrial tissue biopsies were taken from the subplacental site of the uterine wall of term pregnant uteri at the time of delivery by cesarean section. Small pieces of these tissues were fixed in 6 per cent ice-cold, phosphate-buffered (pH 7.4) formaldehyde-glutaraldehyde fixative containing 0.02 per cent trinitrophenol.[4] Several hours later, the tissues were minced and returned to fresh fixative at 5° C. for up to eight hours; then they were washed overnight in cold phosphate buffer (0.1M) and post-fixed for two hours in a phosphate-buffered 1 per cent osmium tetroxide solution. Tissues were dehydrated in mixtures of cold ethanol and acetone according to the method of Brenner[5] and were then embedded in Epon 812.[6] Thin sections were cut with a diamond knife on an LKB ultramicrotome, mounted on copper grids, and stained with uranyl acetate in ethanol for 20 minutes and lead citrate for two minutes. Sections were examined in an AEI-801 electron microscope.

Observations

The myometrium consists of bundles of smooth muscle cells bound together by varying amounts of connective tissue. Within each bundle, the muscle cells are oriented more or less parallel to each other. Both dark and light muscle cells are seen in each bundle.

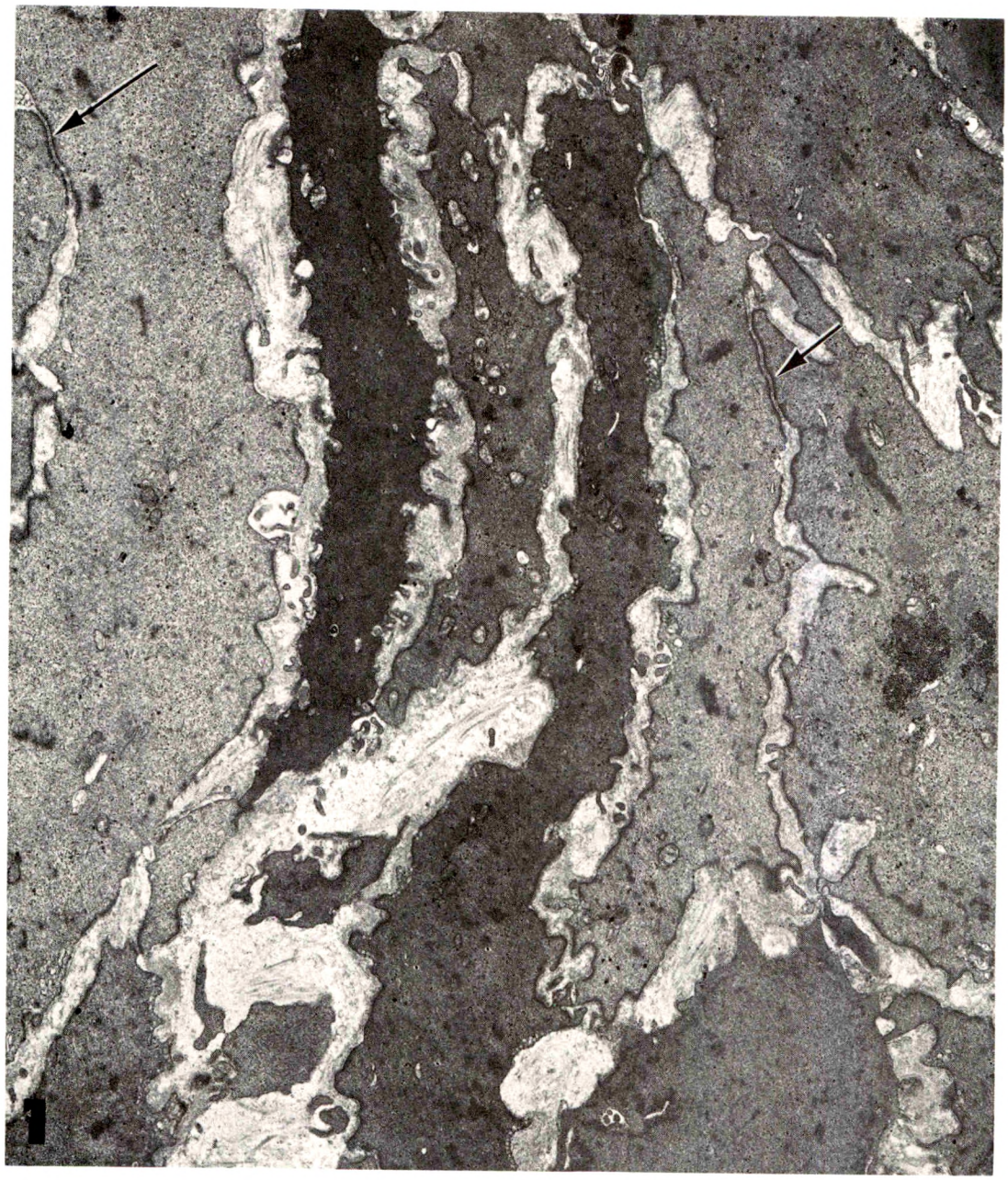


Fig. 1. A bundle of uterine smooth muscle cells showing dark and light muscle fibers. The dark fibers are smaller in size, are widely separated from each other, and exhibit spiny cytoplasmic processes. Light muscle fibers are less separated from each other and exhibit nexuses (arrows) more frequently than dark fibers. (×8,000.)

The dark cells are more electron dense and more irregular in outline with spiny projections and outpouchings. The interspaces between the dark cells are wider and contain more collagen fibers than those between the light cells (Fig. 1). A few small nexuses are occasionally seen between dark cells.

The light muscle cells appear larger than the dark muscle cells in most sections and are separated from each other by narrower interspaces which contain fewer collagen fibers. The neighboring light muscle cells frequently interdigitate through prominent cytoplasmic processes (Fig. 2) and also exhibit more areas of cellular contact (Fig. 1). Pinocytotic vesicles are especially abundant in the cellular process and may be followed for varying distances into the cytoplasm (Fig. 2). The most abundant organelles are the myofilaments which are arranged in bundles of various sizes and are oriented mostly parallel to the long axis of the cell.



Fig. 2. Parts of four light muscle cells are seen in this electron micrograph which shows the abundant interdigitations between cytoplasmic processes of neighboring cells. Note the large numbers of pinocytotic vesicles *(PV)* in these cytoplasmic processes. (×9,000.)

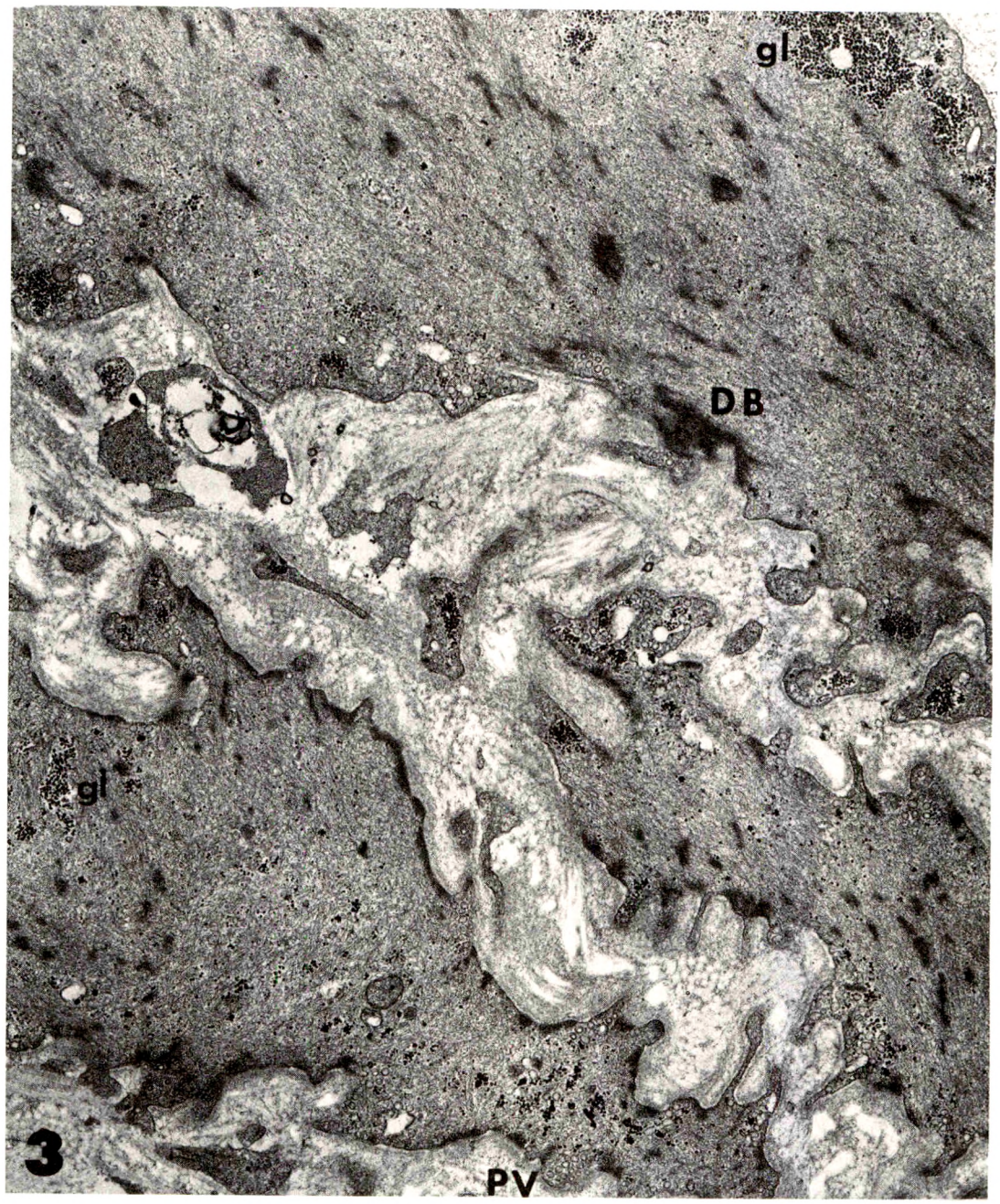


Fig. 3. An electron micrograph of parts of three smooth muscle cells shows the dense bodies *(DB)* and the myofilaments in various directions within the cytoplasm of the same cell. Glycogen particles *(gl)* are scattered randomly throughout the cytoplasm. (×14,500.)

However, myofilament bundles and dense bodies in various directions are frequently seen in the cytoplasm of the same cell (Fig. 3). Other cytoplasmic organelles—mitochondria, Golgi material, and endo plasmic reticulum—are scattered randomly between the myofilaments throughout the cytoplasm.

At the myoendometrial junction, smooth muscle cells are scattered mostly singly or in groups of two or three cells. These cells are mostly elongated, slender, and very irregular in outline because of numerous side cytoplasmic processes of varying sizes and shapes. They are surrounded by large amounts of fine filaments and basement lamina–like material (Fig. 4).

In the basal decidua small groups of large and widely separated cells are seen. They are irregular in outline with short and long processes which come in close

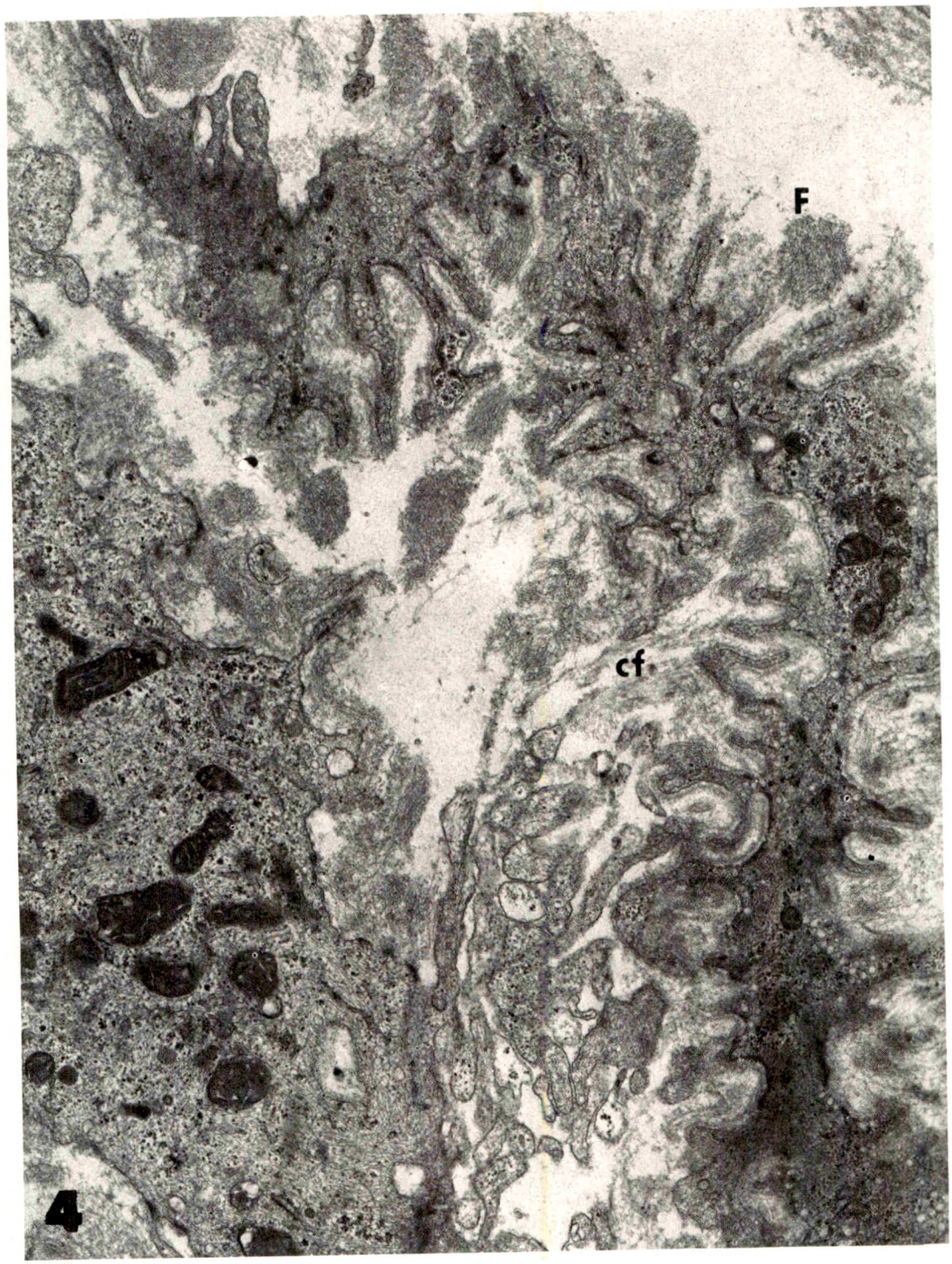


Fig. 4. Occupying the right and upper parts of this electron micrograph is part of a smooth muscle cell characterized by being elongated, slender, irregular in outline and surrounded by large interspaces rich in collagen fibers *(cf)*, fibrin *(F)*, and basement membrane–like material. This type of muscle cell is especially abundant at the endomyometrial junction of the uterus during gestation. (×11,200.)

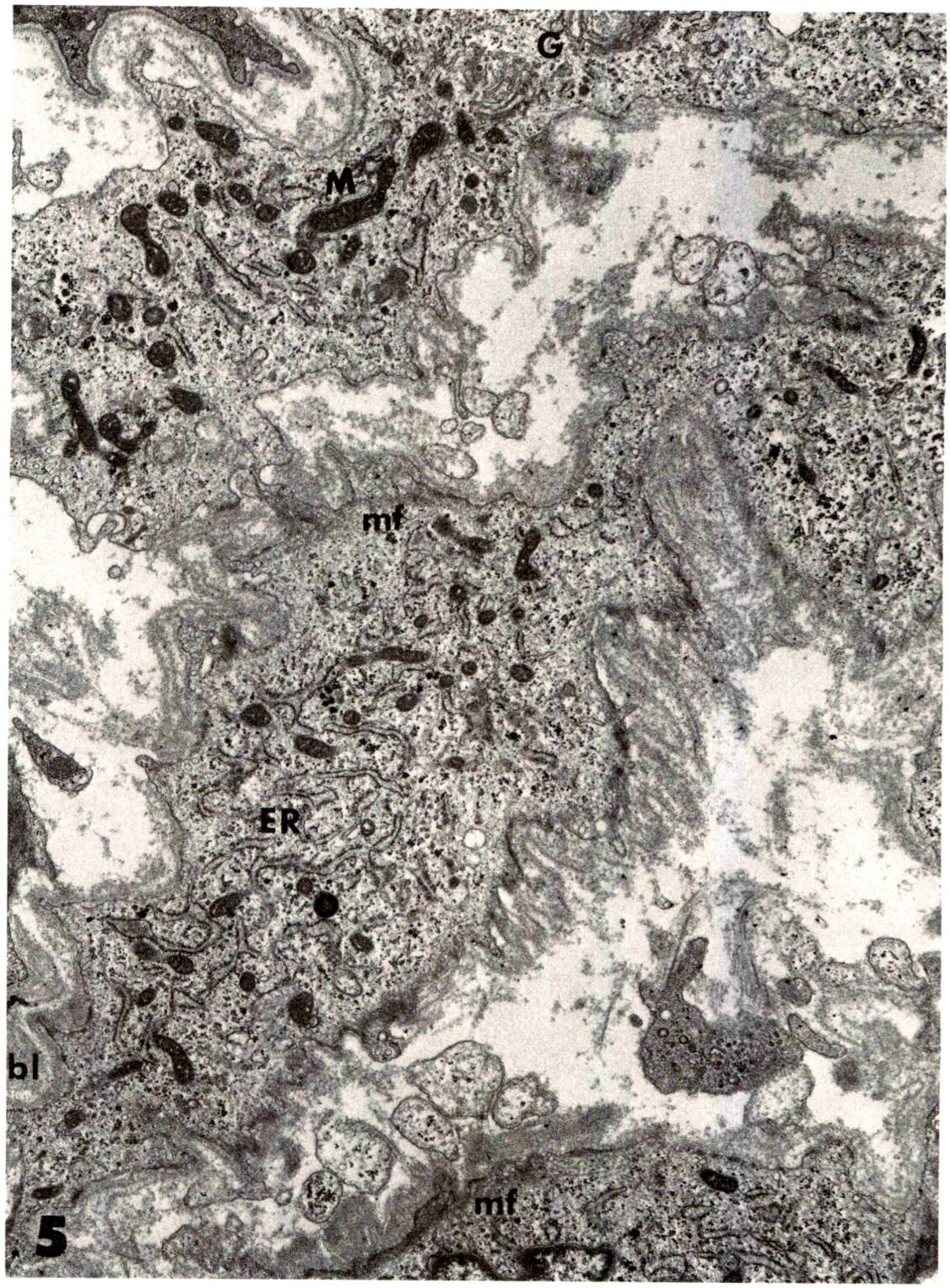


Fig. 5. Highly branched homogeneously low–electron-dense modified smooth muscle cells at the basal decidua contain well-developed endoplasmic reticulum *(ER)*, numerous mitochondria *(M)*, and Golgi areas *(G)*. Myofilaments are loosely and sparsely found throughout the cytoplasm or form very small bundles *(mf)* at the cell periphery under the cell membrane. These cells are widely separated from each other and exhibit well-developed basement laminae *(bl)*. (×11,500.)

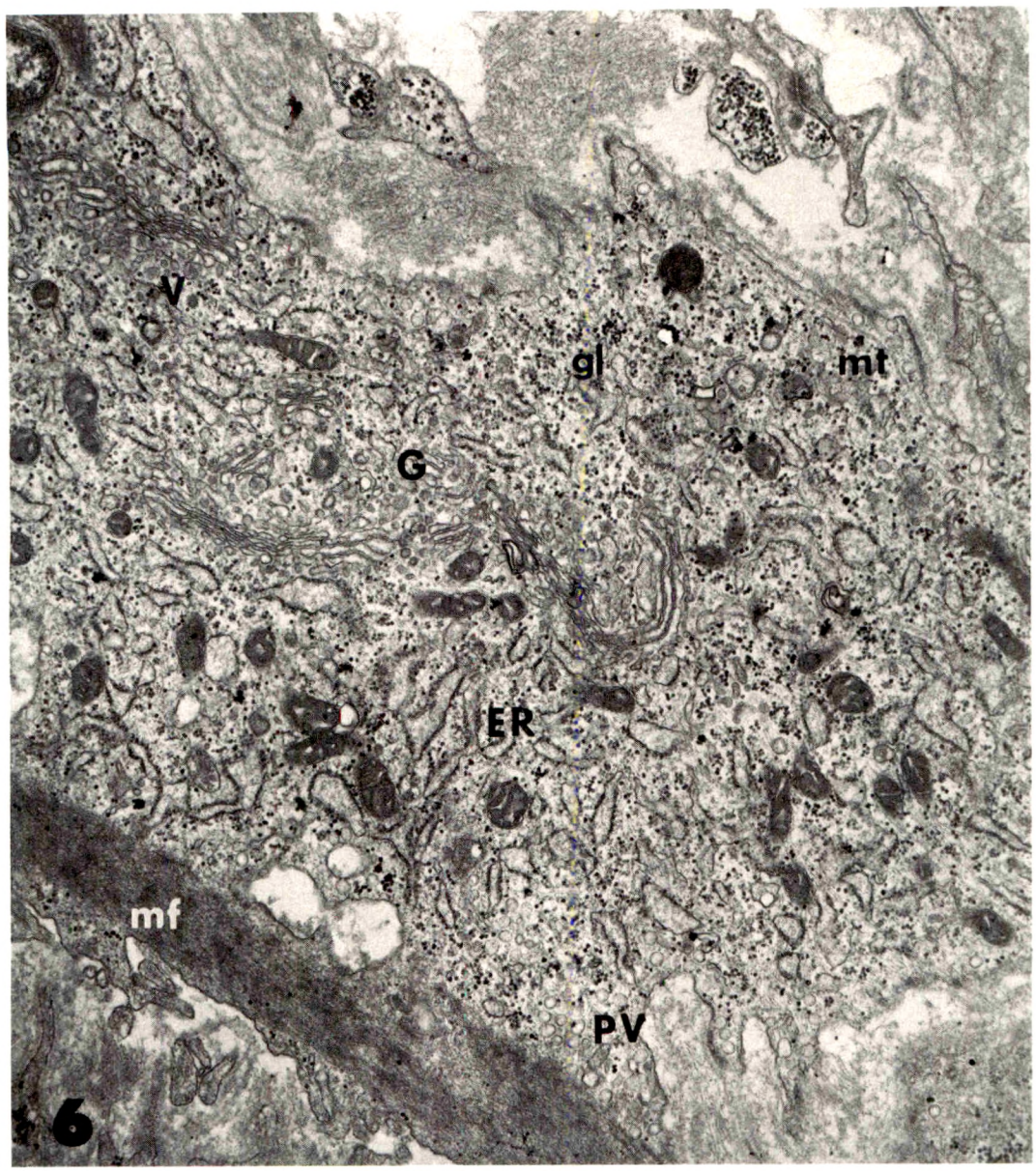


Fig. 6. A well-developed Golgi apparatus *(G)* with associated membrane-bound vesicles containing moderately electron-dense granular or amorphous material is seen in this electron micrograph. Similar material occupies the dilated rough endoplasmic reticulum *(ER)*. Glycogen granules *(gl)*, pinocytotic vesicles *(PV)*, and occasional microtubules *(mt)*, are also seen. Note the presence of a narrow myofilament bundle *(mf)* under the plasmalemma. (×16,000.)

contact with the neighboring cells to form a wide cellular network (Fig. 5). Large interspaces separate the cells and are occupied with abundant amounts of fibrillar and basement lamina–like material. Each cell is surrounded by a well-developed basal lamina and contains numerous pinocytotic vesicles arranged along their border and within the cell processes.

The cytoplasm is diffusely and evenly permeated with organelles, giving the cell a homogeneous low electron-dense appearance (Figs. 5 and 6). Fine filaments of the same diameter as myofilaments are sparsely distributed throughout the cytoplasm. However, narrow bands of such filaments oriented parallel to each other are occasionally seen at the periphery of the cell (Figs. 5 and 6). Mitochondria are numerous, small, and predominantly elongated or oval in shape. Their matrix is more electron dense than the surrounding cytoplasm and contains few lamellar cristae

(Fig. 5). Golgi areas are well developed and occupy large areas of the cytoplasm. They are scattered in small areas throughout the cytoplasm but larger areas are mostly seen near the nucleus (Fig. 6). Parallel stacks of membranous cisternae, vacuoles, membrane-bound electron-dense granules, and clear and coated vesicles are present in and around most of the Golgi areas. Granular endoplasmic reticulum is abundant in the cytoplasm and consists of long branching cisternae, dilated irregular membranous sacs, or short flattened cisternae (Figs. 5 and 6). The membranes are mostly sparsely studded with ribosomal granules, and the lumina are occupied by a finely granular or amorphous substance (Fig. 6). Agranular endoplasmic reticulum is so infrequently seen that it is difficult to differentiate between this organelle and some of the Golgi areas. Free ribosomes are sparsely scattered throughout the cytoplasm, especially near the granular endoplasmic reticulum. Glycogen particles are numerous and are distributed randomly in the cytoplasm (Figs. 5 and 6).

Comment

Dark smooth muscle cells have been described as early as 1900 by Henneberg[7] who thought that the light cells constituted the contracted muscle cells. In 1909, McGill[8] reported that contracted muscles consist mainly of dark cells whereas relaxed muscles consist of light cells. Gansler[3] described light and dark muscle cells in the human uterus and concluded that as strips of myometrial muscle contract an increasing number of dark cells are seen. The present study demonstrates that both dark and light cells are present in the same muscle bundles and that the dark cells exhibit varying degrees of electron density. Dark cells appear smaller in some diameters, exhibit spiny processes and outpouching, and are separated from each other and other neighboring cells by wider interspaces which are occupied by more connective tissue fibrils.

It has been reported that during muscle contraction cytoplasmic fluids seem to flow out into the interspaces as the cytoplasmic organelles become more tightly packed together and the cell becomes darker.[9, 10] The changes in cellular dimensions and the increase in the size of the interspaces observed in this study support this conclusion. The flow of cellular fluids into the interspaces would be facilitated by the large number of pinocytotic vesicles permeating the cell processes and appearing at the surface of the cell as shown in this study.

Myofilaments are not always oriented parallel to the long axis of the muscle cell in contrast to the standard description of such organelles in textbooks. In fact, numerous myofilament bundles in various orientations are seen in the same, as well as in neighboring, cells, especially in the dark muscle cells. This observation does not support the prevalent concept that the smooth muscle cell contracts mainly by shortening its longitudinal diameter. Instead it would be more feasible to assume that all the diameters of the muscle cell undergo some change during muscular contraction. This would result in a more efficient contraction of the hypertrophied and irregular muscle cells of the myometrium of pregnancy.[1] Although there is a decrease in the volume of individual muscle cells during contraction, there is an increase in the volume of the interspaces, probably through the flow of cytoplasmic fluids from the cell into the surrounding interspaces.[10] This is a reversible process which causes the muscle cells to increase in diameter and the interspaces to decrease in size during relaxation. At the same time, there is a decrease in uterine diameter as labor progresses, and this decrease is maintained between uterine contraction, the so-called muscle retraction. This can be accomplished satisfactorily if the muscle cells, as well as bundles of muscle cells, are displaced relative to each other during contraction and do not completely return back to their original positions. The thinning of the lower uterine segment and the thickening of the upper segment, which reach their maximum after the expulsion of the products of conception, seem to be a result of such muscle cell displacement. Since muscle cell contraction affects all its diameters, the cellular movements could be in various directions, namely, longitudinally upward, obliquely upward, or transversely, within the myometrium. Widening of the interspaces as the cells decrease in volume (become dark) will facilitate cellular displacement during contraction. As the contraction comes to an end, the muscle cells increase in size (precontraction size) and occupy more interspace, presumably through the influx of tissue fluid into the cell. This results in reduction of the interspaces, creation of more areas of cellular contacts (or junctions), and extensive interdigitation between the neighboring cells. Thus, the cells seem to be locked or interlocked in their new positions, maintaining the new status affected by the previous contraction of the myometrium.

Modified smooth muscle cells in the basal decidua constitute a network of large cells that are capable of contraction since they contain a small number of loosely arranged myofilaments. In this location they form a buffer zone between the strongly contracting myometrium and the noncontracting decidua and placenta. This buffer function may be accomplished through the creation of some degree of muscular tonus

in the modified smooth muscle cell layer which can absorb a good part of the intensity of myometrial contraction, thus reducing the danger of abrupt changes between the contracting and noncontracting layers of the uterine wall. Therefore, we could assume that this layer of modified smooth muscle cells may be of importance in preventing premature separation of the decidua and trophoblast during uterine contractions in the course of labor. Cells believed to be of smooth muscle cell origin have been described in the walls of the mesometrial arteries.[11] Their physiologic role in this location is not fully understood. Similar cells have been described in the walls of spiral arterioles of the pregnant human uterus and are believed to have a role in reducing the velocity of arterial blood carried through these vessels.[12]

The modified smooth muscle cells exhibit some of the cellular characteristics of secretory cells. They contain an elaborate system of Golgi areas, well-developed granular endoplasmic reticulum, and numerous small mitochondria. The mitochondrial matrix is dense and contains lamellar cristae. Free ribosomes are not significantly numerous in the cytoplasm of these cells. These cytoplasmic characteristics are common findings in cells engaged in protein synthesis for extracellular transport. Modified smooth muscle cells may be involved in synthesis of some of the extracellular ground substance and fibrillar material which constitute a barrier against continued trophoblastic invasion of the maternal tissues during pregnancy. The possible roles of basal decidual cell population in ovum implantation, nutrition, and fetomaternal immunologic relationships have been suggested.[13] Further studies are definitely needed to elucidate the complex nature of cellular population and interaction in this vital part of the uterine wall in early, as well as late, pregnancy.

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Reproductive performance of women successfully treated for gestational trophoblastic tumors

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The reproductive performance of 36 women who had been successfully treated for gestational trophoblastic tumors with multiple courses of cytotoxic agents including methotrexate, 6-mercaptopurine, actinomycin D, and 6-azauridine, between 1962 and 1972, has been studied in comparison with 36 patients who had spontaneously aborted a hydatidiform mole but received no treatment and a control group consisting of 36 women attending an antenatal clinic. The majority of patients who wanted further pregnancies following chemotherapy had one or more successful conceptions. The incidence of abnormal pregnancies in the treated group was higher than that of the control group. Similarly, there was a higher number of abnormal pregnancies in the untreated mole patients when compared with the control group. This suggests that patients who develop trophoblastic tumors tend to have a poor obstetric history and that this is not significantly worsened by chemotherapy.

THE SUCCESSFUL THERAPY of gestational trophoblastic tumors has resulted in an increased number of long-term survivors; many young women so treated have subsequently become pregnant. The principal agents used in treatment possess significant mutagenic and teratogenic potential, but there have been reports in the literature describing successful pregnancies following treatment for trophoblastic tumor[1–3]; therefore, detailed studies of these patients and their children have been undertaken.

Of 258 patients who had received successful treatment for gestational trophoblastic tumors in the Department of Medical Oncology at the Charing Cross Hospital (Fulham) between 1962 and 1972, there were 63 (24.4 per cent) who were known to have had subsequent pregnancies, and 36 of them were available for study.

A questionnaire was forwarded to the 36 treated patients who were asked to attend the hospital with any children born to them subsequent to chemotherapy. At the same time, 36 patients who had spontaneously aborted a hydatidiform mole but who had received no cytotoxic chemotherapy were contacted in a similar fashion; all of these patients were followed with regular estimations of urinary chorionic gonadotropin (HCG) titers by radioimmunoassay following evacuation of the moles.

Both groups were questioned about their reproductive performance before and following the development of trophoblastic disease. Relevant details included the number of abortions, stillbirths, and abnormalities during pregnancy and labor together with the number of premature births and fetal abnormalities. The family doctor and gynecologist of each patient were informed of the project, and they were requested to send further information on obstetric details of their patients where this was unavailable.

There were 35 Caucasian and one Negro Patient among the treated group, and the 36 patients with hydatidiform mole were all Caucasian.

In the treated group, a morphologic diagnosis of choriocarcinoma was established in four patients and invasive mole was diagnosed in four others; 28 were classified as having a trophoblastic neoplasm of unknown histologic type (PTN) on the basis of raised plasma and urinary values of HCG and appearances consistent with a trophoblastic neoplasm on pelvic

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Table I. Details of gestational trophoblastic disease in the treated group of patients

Type	*No.*
Histologically proved diagnosis	
Choriocarcinoma	4
Invasive hydatidiform mole	4
No histologic diagnosis: Persistent trophoblastic neoplasm	
Following hydatidiform mole	26
Following ectopic pregnancy	1
Following missed abortion	1
Total	36

Table II. Age breakdown of treated patients, untreated patients with hydatidiform mole, and control group

Patients	*Age*	
	Range (yr.)	*Mean (yr.)*
Treated	21-43	29
Untreated	18-42	27
Control	18-43	29

Table III. Treated patient group: Pregnancies prior to development of trophoblastic disease

Type	*No. of pregnancies*	*Comment*
Live births	15 (57.7%)	
Stillbirths	2 (7.7%)	Both anencephalic
Abortions	8 (30.8%)	
Premature births	0	
Ectopic pregnancy	1 (3.8%)	
Total	26	

Table IV. Treated patient group: Pregnancies subsequent to chemotherapy for trophoblastic neoplasm

Type	*No. of pregnancies*	*Comment*
Live births	45 (70.3%)	
Stillbirths	4 (6.3%)	2 anencephalic
Abortions	10 (15.6%)	
Premature births	5 (7.8%)	
Total	64	

Table V. Untreated patient group: Pregnancies prior to development of hydatidiform mole

Type	*No. of pregnancies*	*Comment*
Live births	30 (79%)	
Stillbirths	2 (5.3%)	1 Hydrocephalic
Abortions	4 (10.5%)	
Molar pregnancies	1 (2.6%)	
Premature births	1 (2.6%)	Died after 18 hr.
Total	38	

Table VI. Control group: Number and type of pregnancies

Type of pregnancy	*No.*	*Comment*
Live births	70 (87.5%)	
Stillbirths	2 (2.5%)	1 Hydrocephalic with spina bifida
Abortions	3 (3.75%)	
Premature births	3 (3.75%)	
Ectopic pregnancies	2 (2.5%)	
Molar pregnancies	0	
Total	80	

arteriography. Of these 28 patients, 26 had a history of hydatidiform mole four to 44 weeks (mean, 16) previously; one followed an ectopic pregnancy and one followed a missed abortion. Pulmonary metastases were identified in 11 patients and vaginal metastases were present in four (Table I).

Treatment consisted of methotrexate and folinic acid alone in 18 patients; 10 were treated with a combination of methotrexate and 6-mercaptopurine; three received methotrexate, folinic acid, and actinomycin D, and four were given a combination of 6-azauridine, methotrexate, and folinic acid.

Control group. The control group consisted of 36 patients attending an antenatal clinic; they were matched for age with the two study groups but were otherwise selected at random. There were 35 Caucasian and one Negro patient in the control group.

Results

The ages of the patients and control group at the time of the study are shown in Table II. Of the 36 patients in the treated group, six (16.0 per cent) found difficulty in achieving a pregnancy following treatment. Table III shows the number and types of pregnancies in the treated patients prior to the development of the trophoblastic neoplasm. Table IV indicates the number and types of pregnancies in the treated group subsequent to chemotherapy. Table V shows the number and types of pregnancies in the untreated group of patients prior to the development

Table VII. A comparison between the reproductive performance of the untreated patients with hydatidiform mole and the control group

Group	*No. of live births*	*No. of abnormal births*	*Total*
Untreated patients	30 (79%)	8 (21%)	38*
Control	70 (87.5%)	10 (12.5%)	80*
Total	100	18	118

*Chi-square value = 6.605; $p < 0.2$.

Table VIII. A comparison between the reproductive performance of the treated group prior to chemotherapy and the control group

Group	*No. of live births*	*No. of abnormal births*	*Total*
Patients before treatment	15 (57.7%)	11 (42.3%)	26*
Control	70 (87.75%)	10 (12.5%)	80*
Total	85	21	106

*Chi-square value = 86.6; $p < 0.001$.

Table IX. A comparison between the reproductive performance of the treated group after chemotherapy and the control group

Group	*No. of live births*	*No. of abnormal births*	*Total*
Patients after treatment	45 (70.3%)	19 (29.7%)	64*
Control	70 (87.5%)	10 (12.5%)	80*
Total	115	29	144

*Chi-square value = 27.08; $p < 0.001$.

of the hydatidiform mole. Table VI shows the number and types of pregnancies in the normal control group.

By means of the chi-square test, the obstetric details of the treated and untreated patient groups were compared with those of the control group; the number of stillbirths, spontaneous abortions, and premature births were combined under a heading of abnormal births. A comparison was made between the reproductive performance of the normal control group and the untreated patients with hydatidiform mole in Table VII, with the treated group prior to chemotherapy in Table VIII, and the patients following treatment in Table IX. In Table X, a comparison is made between the reproductive performance of the untreated group and the treated group prior to chemotherapy. Table XI provides a comparison between the reproductive performance of the untreated patients with hydatidiform mole and the treated group after chemotherapy. Table XII compares the obstetric details of the treated group of patients before and after chemotherapy. It will be seen from these tables that there was a significant difference in the reproductive performance of the treated group both before and after chemotherapy when compared with the control group.

Table XIII shows the complications that arose during pregnancy and labor in the patient group following treatment. Five patients developed pre-

Table X. A comparison between the reproductive performance of the treated group before chemotherapy with that of the untreated group before onset of the hydatidiform mole

	No. of live births	*No. of abnormal births*	*Total*
Patients after treatment	15 (57.3%)	11 (42.3%)	26*
Untreated group	30 (79%)	8 (21%)	38*
Total	45	19	64

*Chi-square value = 27.4; $p < 0.001$.

Table XI. A comparison between the reproductive performance of the treated group after chemotherapy with that of the untreated group before onset of the hydatidiform mole

	No. of live births	*No. of abnormal births*	*Total*
Patients after treatment	45 (70.3%)	19 (29.7%)	64*
Untreated group	30 (79%)	8 (21%)	38*
Total	75	27	102

*Chi-square value = 4.57; $p < 0.05$.

Table XII. A comparison of the reproductive performance of the treated group before and after chemotherapy

Patients	*No. of live births*	*No. of abnormal births*	*Total*
Before treatment	15 (57.5%)	11 (42.3%)	26*
After treatment	45 (70.3%)	19 (29.7%)	64*
Total	60	30	90

*Chi-square value = 7.46; $p < 0.1$.

Table XIII. The complications of pregnancy and labor in the treated group in pregnancies occurring after treatment

Complication	*No.*	*Comment*
Pre-eclamptic toxemia	5	One premature birth was associated with severe pre-eclamptic toxemia
Placenta previa	2	
Postpartum hemorrhage	2	
Medical induction of labor	2	Labor failed to progress in one and was successfully completed by surgical induction
(infusion oxytocin)	2	
Forceps delivery	4	Three of these were for fetal distress and one was for a persistent occipitoposterior position
Cesarean section (LSCS)	5	Indications were: 1 placenta previa, 1 Breech with fetal distress, and 3 with hysterotomy scars

Table XIV. Pediatric details—age and sex breakdown

	Age			
Sex	*0-6 Months*	*7-12 Months*	*13-60 Months*	*6-9 Years*
Male	3	4	16	1
Female	7	—	10	4
Total	10	4	26	5

Table XV. Details on premature births

	Birth weight grams	*Comment*
J. A.(2)	907	The mother developed severe Pre-eclamptic toxemia and renal failure during her pregnancy
P. B.(3)	482	
M. H.(12)	1,418	Breech delivery
M. K.(19)	1,316	Infant jaundiced at birth
K. J.(24)	482	The uterus was scarred and deformed from previous trophoblastic disease; the infant died 18 hours after birth

eclamptic toxemia; in one case, this resulted in a premature birth. Two patients experienced postpartum hemorrhage, and two presented with placenta previa. Forceps delivery was carried out in four patients, the indication in three of these cases being for fetal distress and in one for a persistent occipitoposterior position. A lower-segment cesarean section (LSCS) was performed in five cases; the indications for LSCS were placenta previa in one case, breech presentation with fetal distress in the second, and the presence of a previous hysterotomy scar in the remaining 3 cases.

Pediatric details. There were 45 children born to the patients in the treated group of which 24 were male and 21 were female (Tables XIV to XVI). Their ages ranged from one month to eight years and nine months; the age and sex breakdown is shown in Table XIV.

As will be seen from Table XVI, among the children born subsequent to chemotherapy, there was one hydrocephalic infant with spina bifida, one case of dolichocephaly and bilateral talipes equinovarus, and one infant with a large umbilical hernia. There were two anencephalic stillborn infants; it is of interest that one of these patients, Case 15 (J. J.), had given birth to an anencephalic stillborn infant prior to the development of the trophoblastic tumor. Finally, in Case 25 (Patient J. M.), the only patient to conceive within six months of completing treatment, the infant developed desquamating fibrosing alveolitis one month after birth.

Table XVI. Fetal abnormalities

Case No.	*Abnormality*	*Courses*	*Drug**	*Total dose (mg.)*	*Method of administration†*
14 (L. H.)	Umbilical hernia	6	MTX, FA	1,200	IM
				144	IM
20 (R. W.)	Spina bifida, hydrocephalus	9	MTX, FA, 6-MP	1,100	IA
				636	IM
				8,800	PO
27 (D. M.)	Dolichocephaly, bilateral talipes equinovarus	7	MTX, FA	700	IA
				330	IM
3 (P. B.)	Anencephalic stillbirth	4	MTX, FA	800	IM
				56	IM
15 (J. J.)	Anencephalic stillbirth	5	MTX, FA	900	IM
				408	IM
25 (J. M.)	Fibrosing alveolitis	5	MTX, FA	960	IM
				110	IM

*MTX = Methotrexate; FA = folinic acid; 6-MP = 6-mercaptopurine.
†IM = Intramusuclarly; IA = intra-arterially; PO = by mouth.

Comment

Hitherto, there have been only two comprehensive reviews of reproductive performance following successful treatment for choriocarcinoma.[4, 5] Van Thiel and associates,[4] in 1970, analyzed 88 pregnancies in 50 women who had been previously treated for gestational trophoblastic neoplasms; there was no increase in fetal wastage, congenital abnormalities, or complications of pregnancy in the patients in their study. Of the 88 pregnancies, there were 71 (81 per cent) term live births, 15 (17 per cent) spontaneous abortions, and two (2 per cent) stillbirths. Reported fetal abnormalities included one child with Pendred's syndrome, one with tetralogy of Fallot, one other child with multiple hemangiomas, eczema, and strabismus, and one stillborn infant with an absent abdominal wall.

In a more recent study, Pastorfide and Goldstein[5] (1973) reported on the reproductive performance of 145 patients who had previously received treatment for a molar pregnancy; 118 pregnancies occurred in 82 of these patients. There were 73 (62 per cent) term live births, one stillbirth, 11 (9.2 per cent) premature births, and 18 (15.1 per cent) spontaneous abortions. Although there was no increased incidence of prematurity, congenital abnormalities, or perinatal or neonatal morbidity in their study, these workers reported a higher rate of spontaneous abortions in those patients who had received treatment with chemotherapy.

It is evident from this and other studies that women treated with cytotoxic agents may subsequently produce normal children. There appeared to be no significant difference in the reproductive performance of the treated group of patients before chemotherapy and afterward. The untreated patients with hydatidiform mole had a better obstetric history when compared with that of the treated group both before and after treatment.

It was also apparent from this study that the number of abnormal births in the control group was significantly lower than that in the untreated patients with hydatidiform mole and in the treated group prior to and following chemotherapy. In contrast to an earlier report,[5] there did not appear to be an increased rate of spontaneous abortions following chemotherapy in this study. Pastorfide and Goldstein[5] (1973) attributed the high rate of abortion in their series to the damage incurred by the genital tract from the previous trophoblastic disease; in one case in our study, a premature birth occurred in a patient who had a scarred and deformed uterus from the previous trophoblastic tumor, and the infant died 18 hours after birth.

The incidence of fetal wastage in the study group following chemotherapy showed a slight increase over that of the normal control group, but a larger series would need to be studied to show a significant difference. The patient who gave birth to a hydrocephalic infant with spina bifida in her first pregnancy following treatment was found to possess 45 chromosomes with a 13/14 translocation on cytogenetic analysis of the peripheral blood lymphocytes by Dr. Sylvia Lawler at the Royal Marsden Hospital. Although the association between hydrocephalus and chromosome anomalies has been observed before,[6] the relationship between the chromosome abnormality in this patient and the occurrence of hydrocephalus and spina bifida in her first child was thought to be entirely

coincidental. The patient had a strong family history of the condition and came from western Ireland where the incidence of neural tube malformations is particularly high.[7] Since the birth of the hydrocephalic infant, she has subsequently given birth to a normal male child who possessed a normal karyotype determined by chromosomal analysis of the peripheral blood lymphocytes.

In a further case in this study, one infant with respiratory symptoms from birth was found, on lung biopsy, to have desquamating fibrosing alveolitis,* the mother having conceived within six months of completing treatment with methotrexate. Desquamating interstitial (fibrosing) alveolitis is a variant of the idiopathic interstitial pneumonias first described by Liebow and colleagues[8] and characterized by massive desquamation and proliferation of alveolar cells into the distal air spaces; it is rare in children, constituting about 10 per cent of the total reported cases.[9] The youngest recorded case of the disease was in a 7-week-old male infant[10]; however, in the case reported in this study, the infant developed symptoms at the age of one month. Methotrexate is retained for up to eight months in the tissues of both animals[11] and man[12]; therefore, the question arises whether the methotrexate administered to the mother of this infant might have played a part in the causation of this rare pulmonary disorder.

The cumulative dosage of chemotherapeutic agents used in the treatment of these patients bore no relationship to subsequent fertility and fetal wastage. There was a higher rate of abnormal births among the treated group of patients when compared with the normal control group, but the numbers were not excessive.

The absence of a notable increase in abnormal births in the treated patients in this study requires further explanation. There is increasing evidence from animal experiments that methotrexate has a deleterious effect on developing ova. It has been demonstrated that the preovulatory phase of oogenesis in mice was most sensitive to the induction of preimplantation egg loss and dead implantations.[13] Further experiments showed that chromosome aberrations induced by methotrexate in the preovulatory phase of oogenesis in mice could be detected in the postovulatory metaphase II oocyte.[14]

In man, there have been many reports on the effects of alkylating agents on ovarian function,[15, 16] but there have been few accounts relating to changes induced by methotrexate and other antimetabolites. In the treated group of patients in this study, pregnancy was proscribed for one year from exposure to these agents, and, as Van Thiel and his associates[4] have suggested, this enforced year of contraception may permit defective ova to be wasted. The agents used in treatment may produce irreparable damage in mature ova, allowing the more immature oocytes to persist and produce gametes for subsequent fertilization.

An alternative explanation for the paucity of abnormalities in those patients who were exposed to chemotherapy is suggested by some recent observations on early embryonic development. It has been estimated that about 25 per cent of fertilized ova fail to implant, presumably as a result of a defective genetic constitution.[17] In addition to this early embryonic loss, the spontaneous abortion rate now falls between 15 and 25 per cent in most surveys.[17] Between 20 and 30 per cent of these spontaneously aborted fetuses are chromosomally abnormal.[18] Roberts and Lowe[20] (1975) suggest that the incidence of malformations in early embryonic life is very much greater than the prevalence of such malformations at birth; the occurrence of genetic mutations leading to congenital defects such as neural tube malformations are now thought to be very common. At the same time, prenatal elimination of these abnormal embryos is considered to be an important factor in their low incidence at birth. The conclusion of these workers is supported by the work of Nishimura[19] who showed that the prevalence of neural tube malformations in specimens from surgical abortions was 10 times greater than the prevalence of these abnormalities at birth.

The possibility of long-term effects of chemotherapy on the gonads of the offspring of the treated patients in this study clearly has to be considered, but evidence will be available only when enough of these children have reached the reproductive age.[21] Therefore, it is important that these children should be observed carefully for a long period. The possibility that some long-term mutagenic effects might be manifest as abnormalities in the second or subsequent generations cannot be excluded and should remain an inhibitory factor against the use of cytotoxic agents in situations where they are not essential such as in the treatment of uncomplicated hydatidiform mole.

It can be concluded from this study that patients with trophoblastic neoplasms tend to have a poor obstetric history, but this was not significantly worsened in those who were treated with chemotherapy. Only four cytotoxic agents were used in the treatment of these patients. It is possible that patients who have had to be treated with a variety of other cytotoxic agents, in

*Hull, D.: Personal communication.

higher dosages and for long periods of time, in order to overcome drug resistance may show additional abnormalities when they are studied.

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Caution: Folic acid may obscure pernicious anemia; the peripheral blood picture may revert to normal while neurological manifestations remain progressive.

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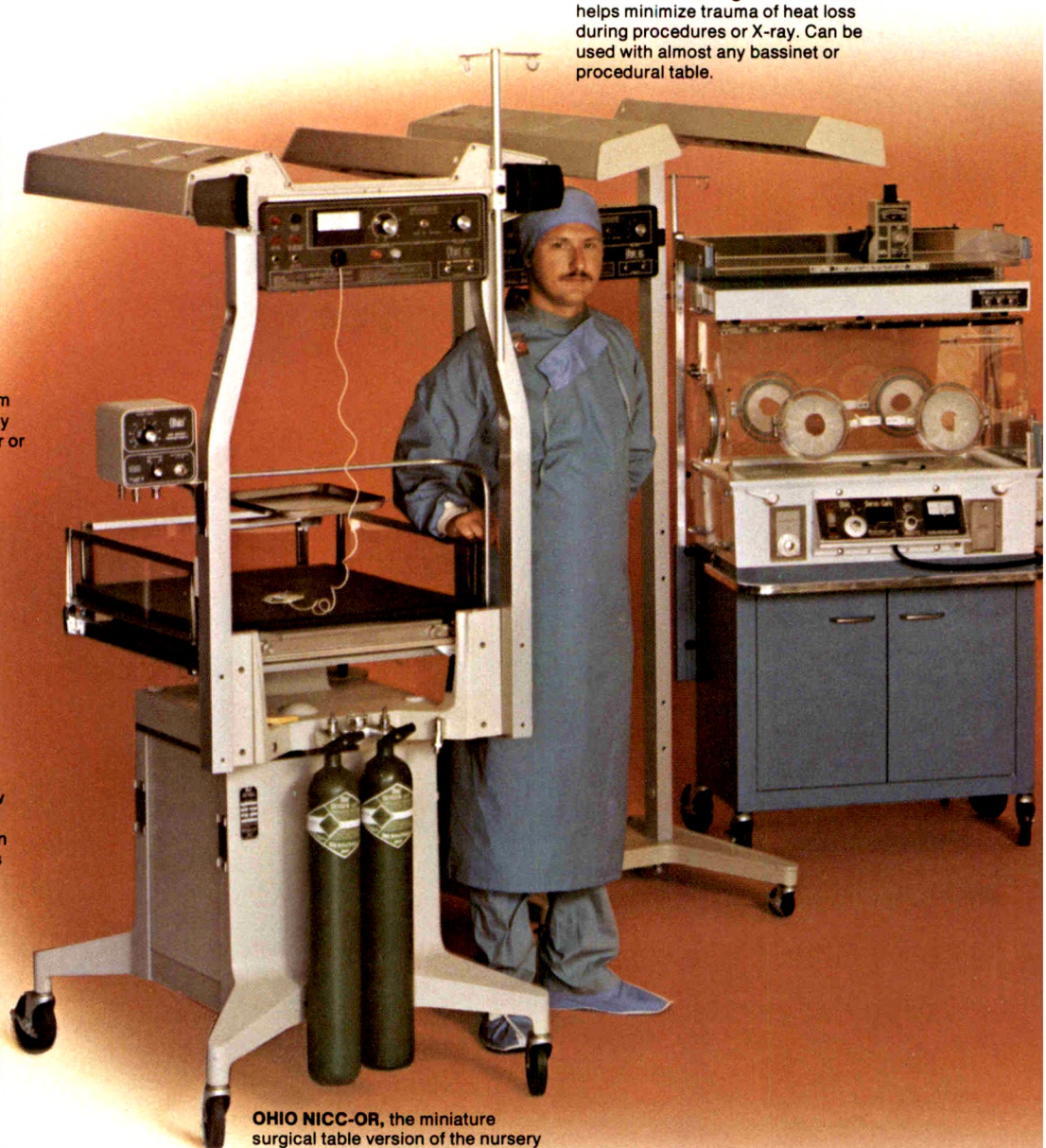


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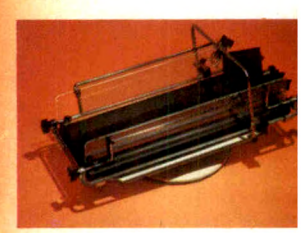
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Serious urinary tract infections usually require immediate treatment. In these cases prudent medical judgment and the use of 'Ancef', when appropriate, can save valuable time while waiting for lab results. 'Ancef' offers:

- **Broad coverage of major urinary tract pathogens**
  E. coli, Proteus mirabilis, Klebsiella species and some strains of enterobacter and enterococci.
- **High urinary levels**
  'Ancef' has been found to achieve peak urine concentrations of approximately 2400 mcg/ml and 4000 mcg/ml respectively following 500 mg and 1 gram IM doses in normal adult volunteers.
- **Convenient IV or IM administration at same dosage schedule**

When lab tests return, if the indicated organism is sensitive to 'Ancef'—and chances are it will be—therapy is already under way. If it isn't sensitive, then 'Ancef' should be discontinued and an appropriate antibiotic selected.

Adverse Reactions
Reported adverse reactions include pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of reported adverse reactions, please see the next page.

Warning: In penicillin-sensitive patients, cephalosporins should be used with caution because of evidence of partial cross-allergenicity of the penicillins and cephalosporins.

Note: In patients with impaired renal function, lower daily dosage is required.

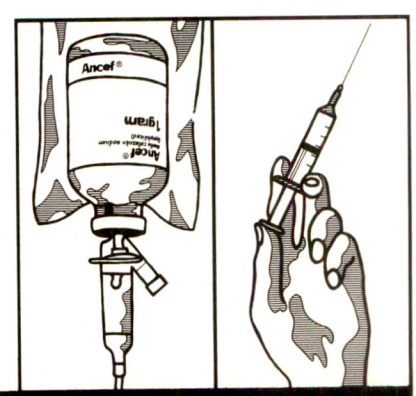
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Injection: 250 mg, 500 mg and 1 gram in 10 ml vials;
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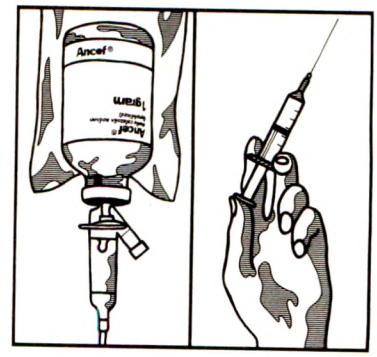


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CEFAZOLIN SODIUM

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido] -5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant).

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus *(P. vulgaris, P. morgani, P. rettgeri)* are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to 'Ancef'.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported.

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible Gram positive cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg.% should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

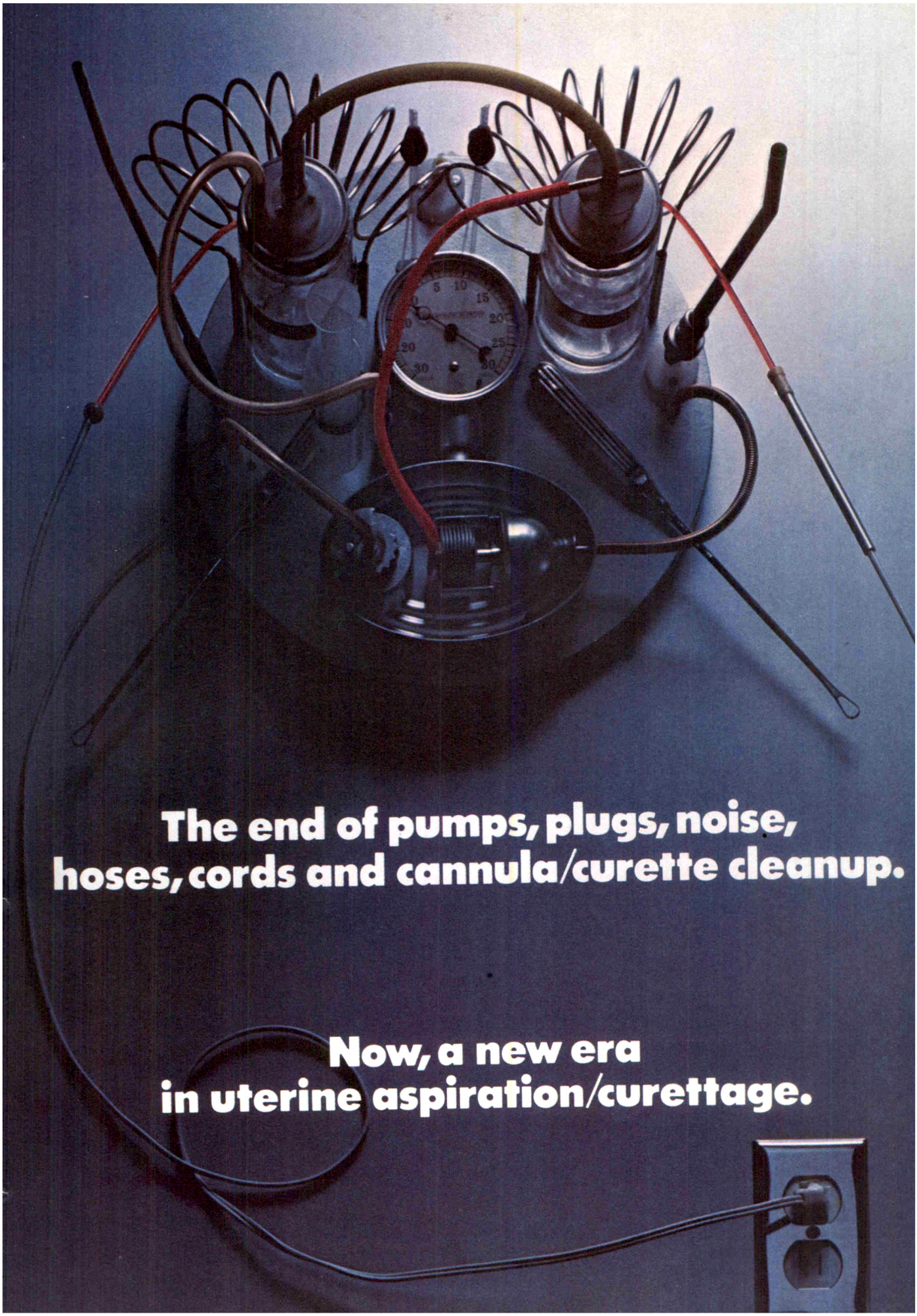
In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

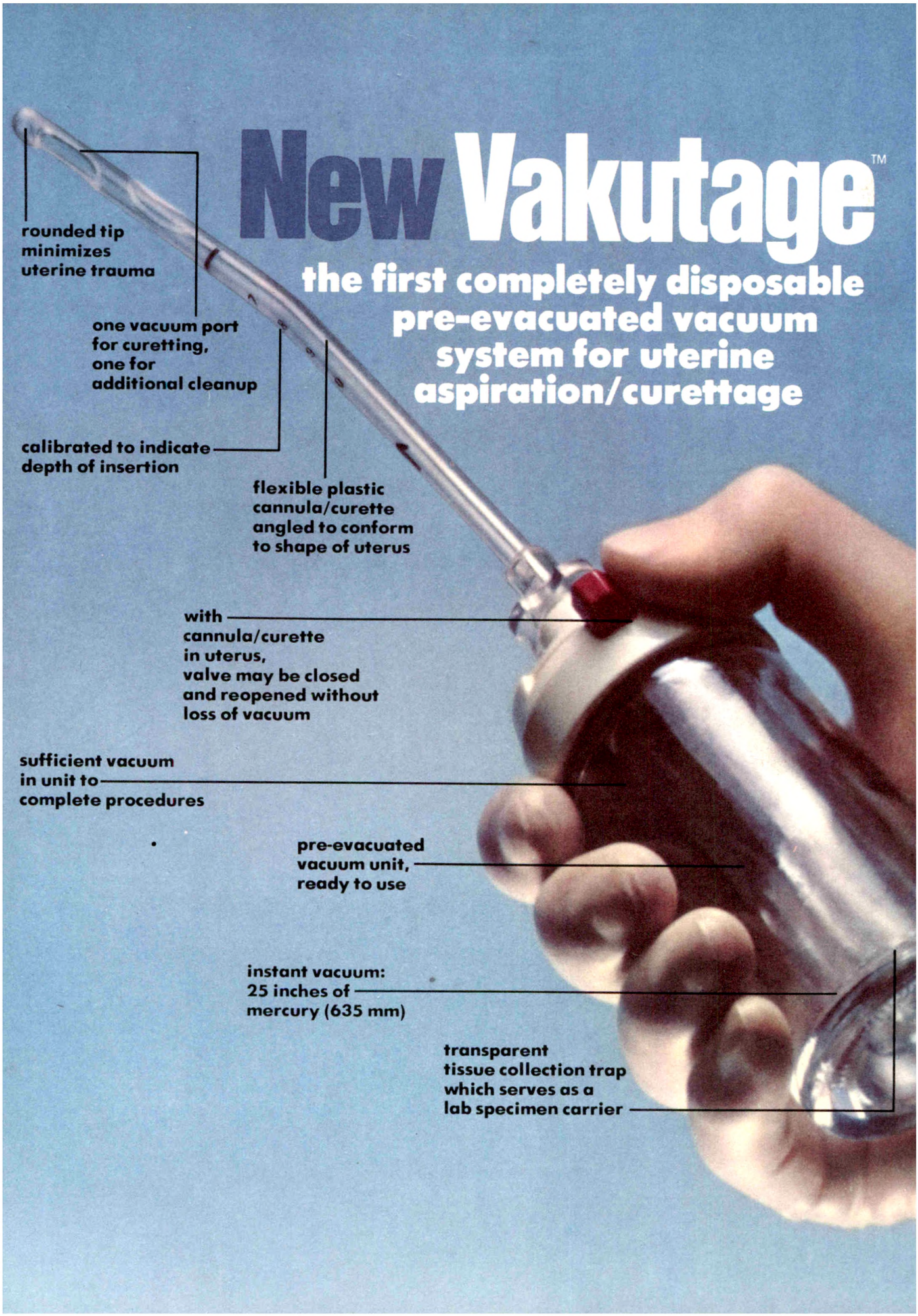
For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F) – supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin; in Overfill ("piggyback") Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 5 grams or 10 grams of cefazolin.

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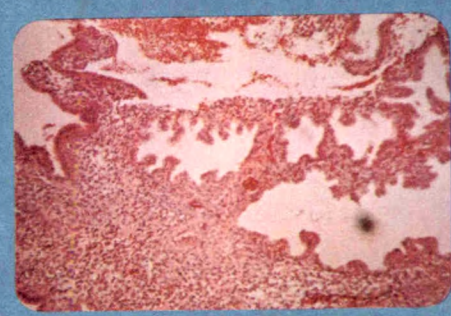
Vakutage is unobtrusive and completely silent when in use—a compact instrument compared to vacuum sources of conventional aspiration equipment.

With Vakutage, local anesthesia and cervical dilatation are usually unnecessary for endometrial biopsy or menstrual induction.

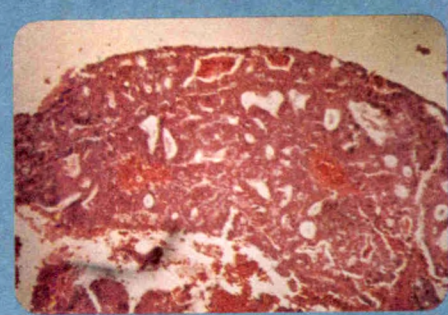
Provides reliable tissue specimens

Unlike the washout technique, biopsy with Vakutage provides intact tissue, not suspended cells.

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Adenocarcinoma of endometrium



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* Data on file at Warner/Chilcott Medical Department.
† In rare instances of inadequate vacuum, the used collection unit can be replaced by another unused one, without removing cannula/curette from uterus.

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FETUS, PLACENTA, AND NEWBORN

Instantaneous fetal heart rate monitoring by electromagnetic methods

K. HUKKINEN, M.S.
V. KARINIEMI, M.D.
T. E. KATILA, PH.D.
H. LAINE, M.S.
R. LUKANDER, M.S.
P. MÄKIPÄÄ, B.S.
Helsinki, Finland

Fetal magnetocardiography (FMCG) is a new complementary external method for accurate antepartal FHR recording. Because of the low magnetic noise level required it is not yet suitable for routine hospital use. Fifty-six simultaneous FMCG and external FECG measurements were made in order to compare these methods for instantaneous FHR recording. The error of the FHR value obtained with the instrumentation described is less than 1 per cent. Our results show that FMCG can be used for FHR processing from week 30 of gestation until term. Thirty-five of the measurements were done during this period. From these, a readable FHR curve was obtained in 21 cases with FMCG and in 12 cases with external FECG. The maternal complexes were always present in the FECG, but in only 15 of the recorded FMCG's.

CONTINUOUS fetal heart rate (FHR) monitoring during pregnancy and labor is routine procedure today in most well-established obstetric units. A recent report estimated that direct monitoring of labor very probably saves a vast sum in public funds by considerably reducing intrapartum fetal brain damage and subsequent mental retardation.[1] In the direct method used during labor the QRS complexes of the fetal electrocardiogram (FECG) are picked up by an electrode attached to the presenting part of the fetus. Signal-to-noise ratio in the direct FECG is good enough for accurate continuous FHR monitoring.

So far, external FHR monitoring is much more problematic than the direct method, yet most authors in this field find estimation of the beat-to-beat variation indispensable also during pregnancy before the actual labor begins.[2] Phonocardiography (PCG) and sonocardiography (SCG, US, or ultrascan) are at present the most widely used methods for external FHR monitoring. Unfortunately, the signals obtained in these methods are heterogenetic and in FHR processing the trigger error too often exceeds one of the parameters to be measured, the FHR variability.

External FECG is another recently used method for

From the Department of Technical Physics, Helsinki University of Technology, and the First Department of Obstetrics and Gynecology, University Central Hospital.

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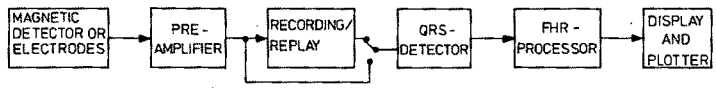


Fig. 1. The arrangement for electromagnetic FHR measurement. The magnetic signal and the electric signal can be obtained separately or simultaneously. Normally the signals are recorded on tape and processed separately later by the QRS detector and the FHR processor. The instantaneous FHR is displayed numerically and plotted on paper. FHR can also be obtained on-line without signal recording.

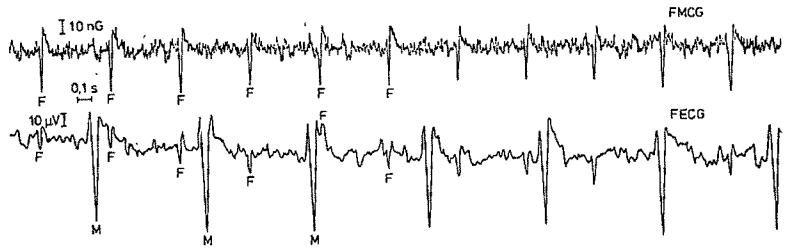


Fig. 2. Simultaneously recorded signals of the FMCG and abdominal FECG from a fetus of 37 weeks. The fetal QRS complexes are denoted *F* and the maternal *M*.

FHR monitoring antepartum; estimation of the FHR variability is possible if the signal is obtained. Its main disadvantage is that the signals are virtually lost between gestation weeks 27 and 34.[3] Our group has previously described a new method for external fetal monitoring, fetal magnetocardiography (FMCG), in which the fetal QRS complexes are detected from above the mother's abdomen with a superconducting magnetometer.[4] Although this technique has its disadvantages, the need for magnetic shielding or an environment with low magnetic noise, we found it important to examine whether it is suitable for use in external fetal monitoring. We present here a FHR processor suitable for use with both the external FECG and the FMCG. We also compare the use of these two methods for instantaneous FHR processing.

Method

The block diagram for electromagnetic FHR recording is presented in Fig 1. The amplified signals can be analyzed on-line or recorded on magnetic tape and analyzed later. The QRS detector detects the fetal QRS complexes and generates a detection pulse when a complex is found. The output of the detector is further analyzed by the FHR processor which also calculates the instantaneous FHR for the plotter and display.

FMCG instrumentation. A gradiometer type magnetometer at liquid helium temperature is used for FMCG measurements.[5] The gradiometer is placed just above the mother's abdomen, close to the fetal heart, without any physical contact with the mother. The magnetic measurement is done in an environment with low magnetic noise without any shielding. It is important that the mother does not have any ferromagnetic materials in her clothing (buttons, zippers etc.). The electronic equipment required for the magnetometer is placed nearby and the rest of the electronics further away to avoid magnetic disturbance. A typical noise level of the magnetic detector using a commercial electronic unit is 0.02 $pT/\sqrt{Hz}$ r.m.s. in the 0.05 to 100 Hz measurement band width. Power line disturbances are eliminated by using a 50 Hz band-reject filter.

FECG instrumentation. The FECG is obtained with four disposable skin electrodes, of which one active electrode is placed just above the symphysis pubis and another on the fundus uteri. One common mode electrode is placed on each flank near the anterior ileal spine. Dead cells are rubbed from the skin and the skin is washed with acetone before attaching the electrodes. Twenty types of electrodes were tested for noise; 18 of them were almost equal and were found to be suitable for FECG measurements. The other two had a considerably higher noise level. The noise of the preamplifier is 6 μV peak-to-peak in the frequency band 3 to 100 Hz. A 50 Hz band-reject filter is also required for the FECG measurements.

The QRS detector. The instantaneous FHR is evaluated from two successive fetal QRS complexes detected by the QRS detector.[6] Because the shapes of the complexes both in the magnetic and the electric signal are almost identical both signals can be analyzed by the same instrument. Signals from a simultaneous magnetic and electric recording are shown in Fig. 2. The letters *F* and *M* denote the fetal and maternal complexes, respectively. It can be seen that the disturbing effect of the maternal complexes is greater

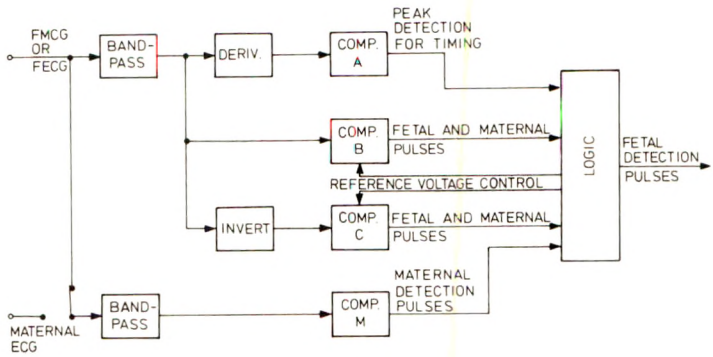


Fig. 3. The QRS detector. The fetal and maternal QRS complexes are examined by comparators B and C. The reference voltages of these comparators are automatically controlled by the logic, which also generates the detection pulses and blocks out pulses due to maternal complexes detected by comparator M.

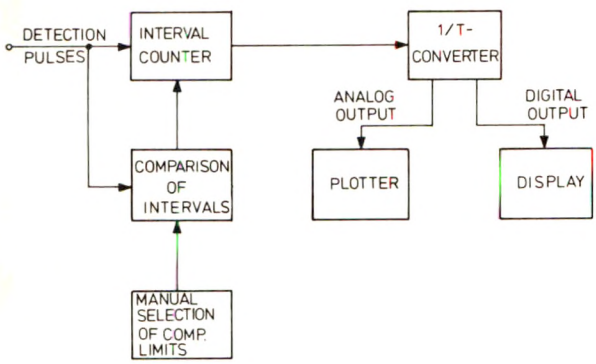


Fig. 4. The FHR processor. The variations between the intervals of successive detection pulses are compared with the manually selected limits. The accepted intervals are converted to beats per minute for analogue and digital output. The blocks for control and timing are not shown in the figure.

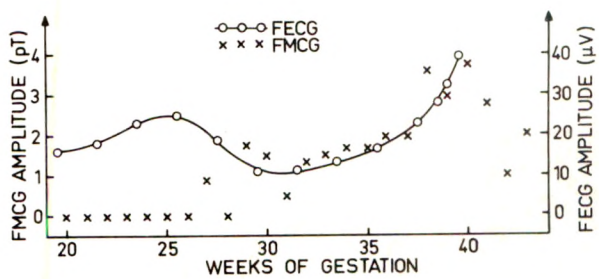


Fig. 5. Correlation between the mean values of the magnetic QRS complexes and the gestation weeks. Bolte's[3] diagram for the electric QRS complexes is presented for reference.

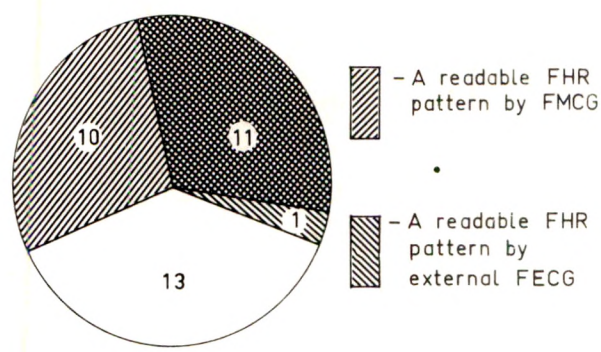


Fig. 6. The results from simultaneous FECG and FMCG measurements. An FHR pattern was obtained in 22 cases out of 35.

in the electric signal. Because of this it is possible to detect all of the fetal complexes only from the magnetic signal. That is why the quality of the FHR curve from the magnetic signal is better than the one obtained from the electric signal.

QRS detection is done by examining the polarity, the duration, and both the positive and negative amplitudes of the possible complexes. Only if all of the conditions set for the fetal QRS complex are fulfilled will a detection pulse be generated. The timing of this pulse is made accurate by separate peak detection. The maternal complexes are detected separately by a method that is based on their greater amplitude in order to block out detection pulses due to maternal complexes. This is usually not necessary when a magnetic signal is analyzed.

The block diagram of the QRS detector is shown in Fig. 3. The signal is first filtered to pass only the main frequency contents of the fetal QRS complex. The positive and negative amplitudes are examined by comparators B and C. The peak of the complex is detected from the derivative of the signal by comparator A. If maternal complexes are present in the signal they are detected by comparator M. The detection pulse is generated from the outputs of comparators A, B, C, and M by a logic circuit. The condition for the approval of a complex is that a pulse from comparator C must be followed by a pulse from

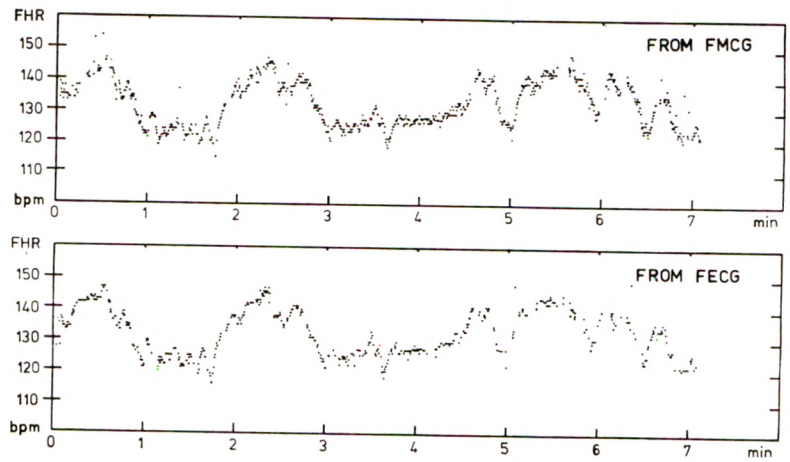


Fig. 7. FHR patterns obtained from the signals presented in Fig. 2. The upper trace (from the FMCG) has more spots than the lower (from the FECG).

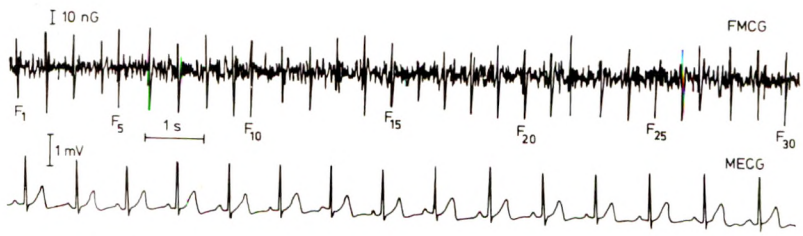


Fig. 8. A FMCG signal with multiple premature beats (upper trace). $F_{5,\ 10,\ 22,\ 27}$ are premature, the intervals preceding them are short and the following intervals are compensatory pauses. The simultaneous maternal ECG is shown for comparison. Gestation week 33.

comparator B within a certain time. The transition of the output of comparator A triggers the detection pulse when the derivative of the signal changes sign.

The FHR processor. The FHR processor compares the intervals between detection pulses and accepts the intervals that are probably due to correctly detected fetal QRS complexes. The processor also converts these intervals to beats per minute (b.p.m.).

The block diagram of the processor is shown in Fig. 4. An interval is accepted only if the corresponding heart rate differs from the previous FHR value by less than ± K b.p.m. K is chosen by the operator: 10, 20, or "no limits." The correct position for this switch depends upon the type of signal (FMCG/FECG), the signal-to-noise ratio, and the amplitudes of the maternal complexes (if any). An accepted interval starts the digital counting of the heart rate, the result of which is converted to analogue form for the plotter. A point plotter is most suitable for the plotting of FHR patterns because it enables easy examination of the beat-to-beat variation. The interval that is to be converted must be between 0.25 and 2 seconds, which corresponds to FHR values from 240 to 30 b.p.m. There is also a digital display of the heart rate, which is turned off if a detection pulse is not received within two seconds.

The error in the FHR value obtained is due partly to the error in the timing of the detection pulse and partly to the error in 1/T-conversion. Together, these introduce a maximum error range of from −1 to +0.6 per cent at full scale.

Patients

Fifty-six simultaneous FMCG and external FECG recordings were made with the instrumentation described. The gestation weeks ranged from 20 to 43. The status of most of the patients was normal, but there were four cases of suspected placental insufficiency. No attempt is made here to draw clinical conclusions from the available data.

Results

QRS amplitude of the FMCG. The mean values of the magnetic QRS complexes are presented in Fig. 5 as a function of gestation. The magnetic complexes began to be detectable at about 30 weeks, the time at which the electric complexes were decreasing. No

decrease of the magnetic signal was seen until after 40 weeks.

FHR obtained from the FMCG and FECG. As stated above, the amplitude of the magnetic QRS complexes is high enough for FHR processing from week 30 on. Thirty-five of the investigated pregnancies belonged to this period. FHR recording succeeded in 12 cases with external FECG and in 21 cases with FMCG, as can be seen in Fig. 6. There were 10 cases where FECG failed but FMCG gave a readable result. In one case a readable pattern was obtained with FECG but not with FMCG. The maternal complexes interfered with the FHR processing in 15 cases out of 35 using FMCG and in all the cases when FECG was used.

Fig. 2 is a simultaneous recording of the abdominal FECG and FMCG. The signal-to-noise ratio in the upper (magnetic) trace is obviously better than in the lower (electric) signal. In the FECG the tall maternal peaks are disturbing. The FHR patterns plotted by the equipment are presented in Fig. 7.

The quality of the FHR curve obtained from the FMCG is better than the one obtained from the FECG because there are more results or spots on the former. In the latter, about 20 per cent of the intervals have been lost because of the coincidental fetal and maternal complexes.

Arrhythmias are known to be problematic for conventional cardiotocographs where sequential variations exceeding a preset value are neglected by logic. This instrument permits manual selection of a "no limits" position, where all intervals between 0.25 and 2 seconds are accepted. Fig. 8 is an FMCG in which there are four premature beats causing a short interval followed by a compensatory pause. The FHR processor is capable of plotting a FHR trace from this FMCG, as shown in Fig. 9. A premature beat causes two successive spots on the FHR curve, one above the normal values, the other below them. Some of these FHR values are about 210 b.p.m., a commonly used upper limit for the commercial cardiotocograph. In Fig. 10 there is another example of an FHR curve with multiple premature beats which disappear during accelerations.

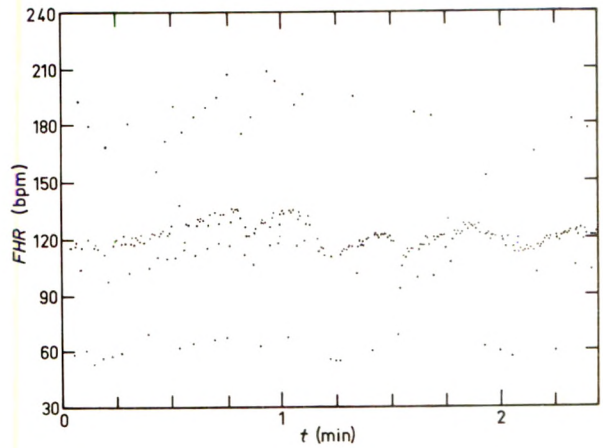


Fig. 9. FHR pattern obtained from the FMCG presented in Fig. 8. Each premature beat causes a spot above the normal value and a successive spot below the normal value. FHR values below 90 b.p.m. are caused by undetected QRS complexes.

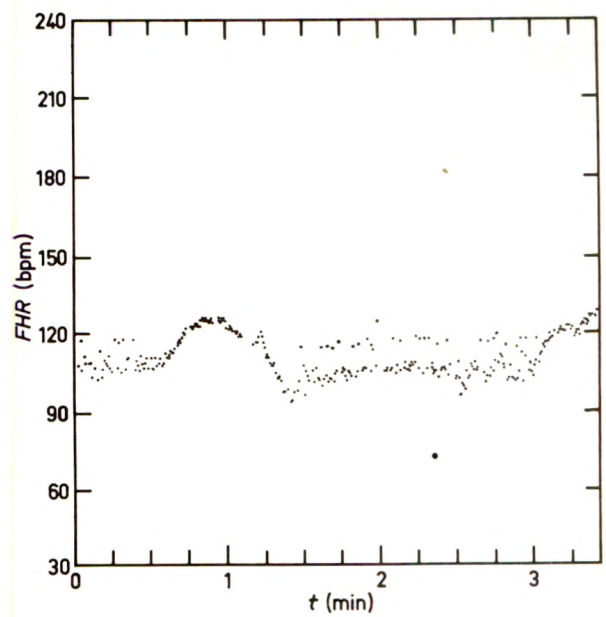


Fig. 10. FHR pattern obtained from the FMCG of the same patient as in Fig. 9, but 2 weeks later (gestation week 35). The premature beats are seen, but they disappear during accelerations.

Comment

Use of the abdominal FECG for antepartum FHR monitoring is seriously limited by the attenuation of the QRS complexes at the beginning of the last trimester. The results of our external FECG measurements confirm this observation.

Our experience suggests that FMCG is a complementary method for external FHR recording, mainly because it is the only additional method of comparable accuracy. With the present instrumentation the magnetic QRS complexes become detectable at the same time that the electric complexes disappear or diminish in size. Whether this phenomenon is a mere coincidence or dependent on a common cause is not yet clear. If attenuation of the electrical QRS complexes is caused by increasing vernix caseosa on the fetal skin, this insulating effect might cause a change in the current

distribution and an amplification of the magnetic fields. The amount of vernix decreases again after term, and in our diagram the size of the magnetic QRS complexes seems to diminish again after 40 weeks of gestation.

When FMCG is compared with external FECG as a means of recording FHR with simultaneous measurements and both are successful, the FHR results agree with a difference no more than 1 b.p.m. Because a heart rate variation of less than 3 per cent is already considered pathologic, the total error of this equipment does not interfere seriously with the estimation of this variation.

Poor signal-to-noise ratio is still a problem in both FMCG and external FECG. Not much improvement is expected in the electric method. However, the signal-to-noise ratio of the magnetic equipment can be considerably improved and such an instrument has already been constructed.[7] Thus FMCG may become a useful screening method in antepartum FHR monitoring, but the problem of magnetic noise must be solved before it is usable in a hospital.

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Sampling the fetoplacental circulation

I. The pregnant ovine

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Intrauterine endoscopy (fetoscopy) was successfully accomplished in 26 specially prepared pregnant sheep at 85 to 110 days' gestational age, with the use of a conventional 2.7 mm. Hopkins straightforward wide-angle telescope (Stortz 27018A) encased in a prototype 3.1 mm. eccentric cannula which incorporates a 25 gauge needle channel. Fetal blood was aspirated in 12 lambs. Twenty-five animals were followed throughout the remainder of pregnancy: nine (36 per cent) aborted within three days—three weeks after endoscopy. The pregnant ovine appeared to be a useful experimental animal model for the development of an intrauterine endoscopy technique.

THE ETHICS OF human experimentation during pregnancy properly restrict the use of a research procedure, modality, device, or material until it reasonably can be expected to have no adverse effect on the fetus. Accordingly, our group determined in July, 1973, to assess the merits and safety of intrauterine endoscopy (fetoscopy) in the pregnant experimental animal model. Primary trials, with several different endoscopes and with the pregnant sheep at different gestational ages, led us to develop a protocol in which pregnant sheep would be specially prepared for endoscopy which would be performed five to seven days later, the fetoplacental circulation would be sampled, and the animals would be followed throughout the remainder of pregnancy. Documentation of this experience in 28 pregnant sheep follows.

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Material and methods

Preliminary efforts at endoscopy in the pregnant sheep at or near term (140 days) were troublesome because of: (1) interposition of the intestines and the omentum between the anterior abdominal parietes and the pregnant uterine horn, and (2) uncertainty as to where the endoscope was being placed, for example, in the nonpregnant horn. Accordingly, after trial and error in 10 animals[1] at varying gestational ages (70 to 140 days), we determined that: (1) the small fetus, gestational age 85 to 95 days, and weight approximately 1 kilogram was surrounded by a sufficient amniotic fluid volume to permit modest fluid losses without seeming compromise to the pregnancy, and (2) some means of fixing the pregnant horn to the anterior abdominal wall would be necessary if a simple transcutaneous, transuterine endoscopic procedure was to be evaluated.

Accordingly, we developed the following marsupialization procedure: in brief, pregnant ewes at an average gestational age of 91 days (range 83 to 103 days) with singleton pregnancies were fasted overnight, anes-

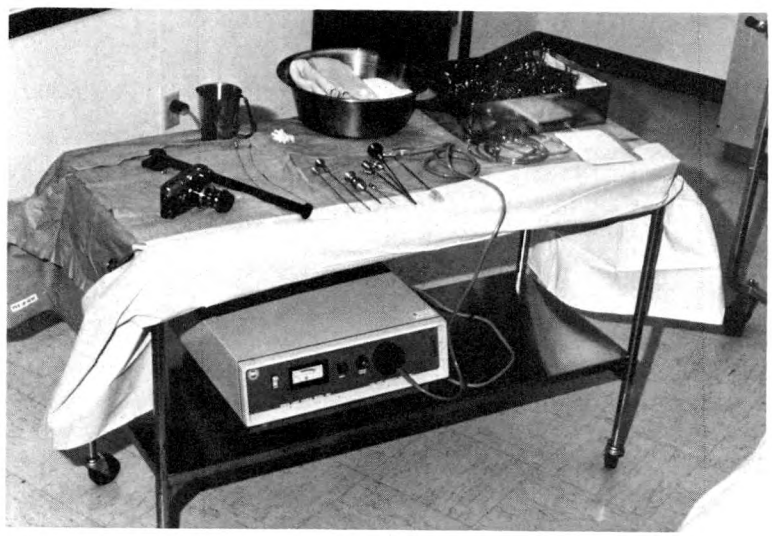


Fig. 1. Endoscopic devices and xenon arc light source used for intrauterine fetoscopy (see text for details).

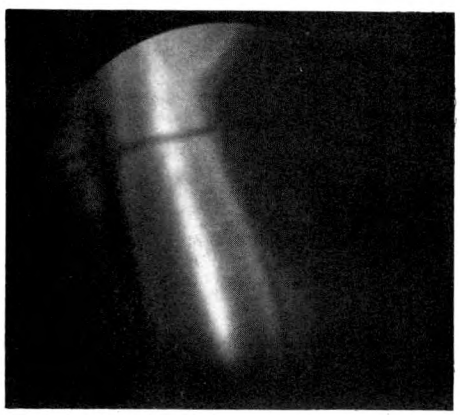


Fig. 2. Typical umbilical venous tributary observed with fetoscope. Arterialization of fetal blood makes distinction from umbilical arterial vessels quite easy.

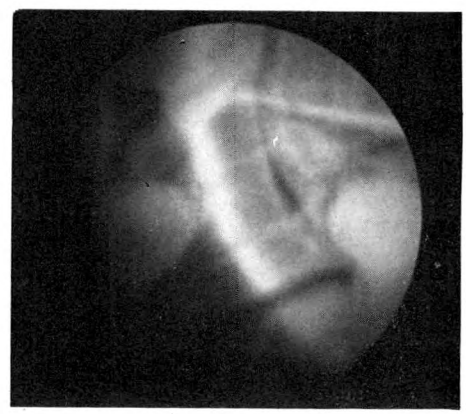


Fig. 3. Umbilical venous tributary infested by amnion with sessile pedunculated squamous metaplastic keratinized nodules.

thetized with intravenous pentobarbital, and maintained on a 50/50 mixture of nitrous oxide and oxygen via a cuffed endotracheal tube. The animal was restrained in the lateral recumbent position with a lower limb abducted. The abdomen was denuded of wool with the depilatory*; a meticulous sterile technique was observed while the abdomen was opened in the midline. When the abdominal cavity was opened, the pregnant uterine horn was identified and a small portion of the wall of this horn was marsupialized with interrupted nonabsorbable sutures to the rectus fascia. The rectus fascia was approximated with interrupted, braided wire sutures except for a 1 to 2 cm. central defect through which the uterus was allowed to herniate. Since the incision in the underlying fascia was placed about 3 cm. parallel to and above the initial skin incision, closing the skin, in fact, covered the uterus. Five to seven days later, the ewe was returned to the surgical pavilion, anesthetized, and prepared for operation. The defect in the rectus fascia, covered only by integument, was easily palpated. A small stab wound was made in the skin overlying the defect, and a specially fabricated eccentric cannula,* 3.1 mm. outside diameter, with a trocar containing a 25 gauge needle channel (Fig. 1) was punched into the pregnant uterine cavity. The trocar was replaced with a 2.7 mm. Hopkins straightforward wide-angle telescope† with incorporated fiber-optic light transmission. A Stortz* xenon

*Nair, Carter Products.

*Karl Stortz.
†27018A, Karl Stortz.

Table I. Outcome of 28 pregnant sheep specially prepared for fetoscopy which was performed about seven days later (range 4 to 11 days)

Sheep No.	Gestational age (days)		Fetoplacental blood sample	Outcome
	Prepared	Endoscopy performed		
181	88	92	Yes	Aborted 5 days post endoscopy
1015	83	87		Aborted 3 days post endoscopy
22	83	90		Aborted 3 weeks post endoscopy
47	92	97		Aborted 8 days post endoscopy
206	86	93	Yes	Aborted 17 days post endoscopy
483	85	96		Aborted 3 days post endoscopy
669	95	99	Yes	Aborted 3 weeks post endoscopy
682	91	95		Aborted 4 days post endoscopy (hernia)
1034	91	98		Aborted 2 days post endoscopy (infection)
161	89	93		Aborted 3 days post endoscopy
211	85	92	Yes	Neonatal death
8	90	97	Yes	Neonatal death
474	92	97		Neonatal death
979	85	92	Yes	Live born
968	90	97		Live born
986	89	93	Yes	Live born
190	94	99	Yes	Live born
219	102	106	Yes	Live born
371	80	85		Live born
376	103	110	Yes	Live born
423	91	96		Live born
485	85	96		Live born
585	93	100	Yes	Live born
612	100	105	Yes	Live born
670	97	101		Live born
17	100	/		Aborted 4 days after marsupialization (infection)
143	94	101		Maternal death (anesthesia) with endoscopy
496	85	/		Failed endoscopy (live born)

Number of animals prepared for endoscopy (marsupialization): 28. Number of animals in which endoscopy was performed: 26. Endoscopy with fetal blood sample was performed in 12 (46 per cent). Number of animals which aborted: nine (36 per cent). Endoscopy only was performed in six. Endoscopy with sampling was performed in three. Maternal death (anesthesia) after endoscopy occurred in one. Neonatal losses (from probable clostridia in nonimmunized animals) occurred in three.

arc light source was joined to the endoscope. A beam-splitting eye piece was attached to the endoscope to permit visualization of the intrauterine contents by an assistant. Still pictures were obtained by coupling the endoscope to a 35 mm. camera* after the detachable camera lens was removed. Ektachrome ASA 160 film† was used and developed by a special "push" process as though exposed at ASA 400; shutter speed varied from F8 to F15. The operator endeavored to manipulate the endoscope into the immediate proximity of a fetoplacental vessel, introduce the sampling needle within the vessel, and aspirate a fetal blood sample into a syringe containing heparin. The needle was then removed from the punctured vessel; bleeding was observed, and the endoscope was removed. Cultures of the amniotic fluid were taken for bacteriologic studies. The defect in the integument (and underlying uterus) was closed with a single transfixion suture.

In each case the operator was limited to a maximum of 30 minutes for the entire endoscopic and/or sampling procedure. After endoscopy had been completed, the animal was returned to its pen. One week later, each survivor was transported by truck to a ranch facility in the Fresno area (250 miles away) where it was followed throughout the remainder of the pregnancy.

*Olympus Corp. of America, Precision Instruments Div., 2 Nevada Dr., New Hyde Park, New York 11040.

†Eastman Kodak Co., 343 State St., Rochester, New York 14650.

Results

Twenty-eight animals were specially prepared as described. One animal experienced a cardiopulmonary accident during endoscopy and died shortly thereafter;

the accident was preventable. Endoscopy was not possible in two animals; one experienced a massive herniation after marsupialization and was killed. The operator was unable to introduce the endoscope within the uterus in the other animal in that he consistently entered the peritoneal cavity, and the procedure was abandoned.

Table I summarizes the operative experience in all 28 animals. Endoscopy was successful in 26 animals but one ewe died immediately thereafter from a preventable anesthetic accident. Fetal blood was obtained in 12 lambs. Either sampling was omitted (nine animals) or the attempt at sampling was unsuccessful (five animals). Most of our early failures were due to our inexperience with the sampling technique.

Twenty-five animals were followed throughout the remainder of pregnancy after endoscopy. Nine of the 25 animals (36 per cent) unexpectedly aborted after endoscopy at varying time intervals (three days to three weeks). Six of these abortions occurred within seven days of endoscopy; the other three animals aborted at eight, 17, and 21 days, respectively. Since these three animals had been transported one week after endoscopy to a ranch facility 250 miles distant, it is possible that this stress contributed to the abortion. Three of the animals that aborted had endoscopy performed, and the lamb was sampled; two of these aborted at 17 and 21 days after the procedure. In summary, a 24 per cent abortion rate (six of 25 animals) within the first week after endoscopy was demonstrated.

Figs. 2 and 3 clearly depict the fetoplacental architecture. The pedunculated, sessile structures are squamous metaplastic and hyperplastic nodules of amnion which often are quite florid in ruminants but have also been found in subhuman primate and human pregnancies.

Fetoplacental blood loss following removal of the sample needle from the punctured vessel was not estimated. However, we were surprised to find that the blood loss appeared to be rapidly contained by what was interpreted to be the presence of thromboplastic substances in the amniotic fluid. The exiting blood appeared to coagulate and pool quickly in the immediate vicinity of the puncture site.

All bacteriologic studies of the amniotic fluid were reported as showing "no growth." No such studies of the abortus or the puerperal ewe were possible.

Comment

We believe this to be the first documentation of the long-term outcome of intrauterine endoscopy (fetoscopy) in any pregnant animal population. Levine and associates[2] described endoscopy in four pregnant sheep, two at term, two at a gestational age of 60 to 70 days. The uterus apparently was exteriorized after laparotomy, and the endoscope was inserted by direct visualization in each case. Three animals then were killed, and one of the ewes, gestational age unspecified, reportedly went uneventfully to term. Levine and associates[2] found, on the basis of this experience, ". . . the sheep to be an inadequate model for visualization of the fetus and for aspiration of fetal blood." We submit that this conclusion was premature and reflects the better optics in the larger endoscope we used (1 mm. larger outside diameter than the Needlescope*), the use of a *separate* biopsy-aspiration instrument, and/or exteriorization of the uterus. Fixing the pregnant horn to the rectus fascia prior to endoscopy clearly proved to be a useful step in our study.

Experimental animal studies are, we believe, essential in the evaluation of any new technology. Pregnancy imposes the additional responsibility of assuring the safety of the procedure to both the mother and the fetus. And it is our concern about the safety of fetoscopy which remains our major objective—and is as yet unresolved. We do not believe that the only adequate model is the pregnant woman—the ultimate model, yes! But the current state of technology seems sufficiently crude and imprecise that fetoscopy should be accomplished in experimental animal models. We suggest that the pregnant ovine, gestational age 85 to 110 days, is such a model. Whether or not the disturbing fetal wastage can be extrapolated to the human patient is speculative but certainly deserves the most serious consideration.

*Dyonics, Inc., 71 Pine St., Woburn, Massachusetts 01801.

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Evaluation of the accuracy of a new ultrasonic fetal heart rate monitor

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An indirect Doppler fetal monitoring system has been developed and validated by computer comparison of simultaneous fetal heart rate (FHR) with Doppler and scalp ECG of high-risk patients during labor. The difference in measurement of FHR averaged 0.3 b.p.m., and 93 per cent of the Doppler FHR measures were within 10 b.p.m. of the ECG FHR. If interinstrument difference is discounted, 96 per cent were within 10 b.p.m. All types of decelerations and variability were well approximated. Doppler FHR from the instrument described may be relied upon as valid clinical information and may be obtained from over 90 per cent of labor patients with 93 per cent accuracy.

THE RECENT increased interest in fetal heart rate monitoring (FM) for ascertaining intrapartum fetal well being and improving fetal outcome has produced a need for simplified and improved FM techniques. The majority of the published studies described a direct fetal electrocardiogram (ECG) monitoring system. Although the direct or internal FM scalp electrode technique may be highly accurate and may entail little patient restriction, it has limitations. Direct monitoring can be applied only after a cervical dilatation of at least 2 to 3 cm. and after rupture of the fetal membranes. The application is somewhat difficult and it requires some skill to correctly attach the electrode, which, furthermore, usually must be applied by a physician. Recently there has been some concern about an increased incidence of postpartum endometritis among patients who have been monitored internally, compared to nonmonitored patients.[1, 2] There have been instances of perforation of the fetal fontanelle, bleeding, and infection associated with the use of fetal scalp electrodes.[3, 4, 6] It is common experience that up to 2.0 electrodes per case may often be required because of electrode misplacement or dislodgement.[7] Electrodes tend to loosen, especially after vaginal examinations and excessive patient motion. Patient agitation may cause interference and produce a poor record. Unusual QRS wave forms may cause erratic counting if care is not taken, and improper placement of the electrode may produce incorrect counting. The maternal ECG has been obtained and the maternal heart rate recorded instead of the fetal heart rate (FHR) in patients with fetal death.[8–10] Maternal and fetal heart rate have been added together, producing a spurious tachycardia.[11] Totally spurious results have also been recorded.[12]

Therefore, there seems to be a need for a reliable noninvasive external or indirect fetal monitoring technique that could be applied in premature labor, or when a patient is admitted in early labor, before rupture of the membranes. It can be applied by the nursing staff, as soon as a patient is admitted to the delivery suite, without the presence of a physician. Although indirect FM's are commercially available, they are regarded as screening tools,[13] perhaps because they may produce a poor yield of usable data, or some erroneous data,[10] and they may be difficult to operate. Emphasis was therefore directed toward the development of a more practical indirect fetal monitoring system by utilizing an improved and more sensitive Doppler ultrasonic technique. This report describes

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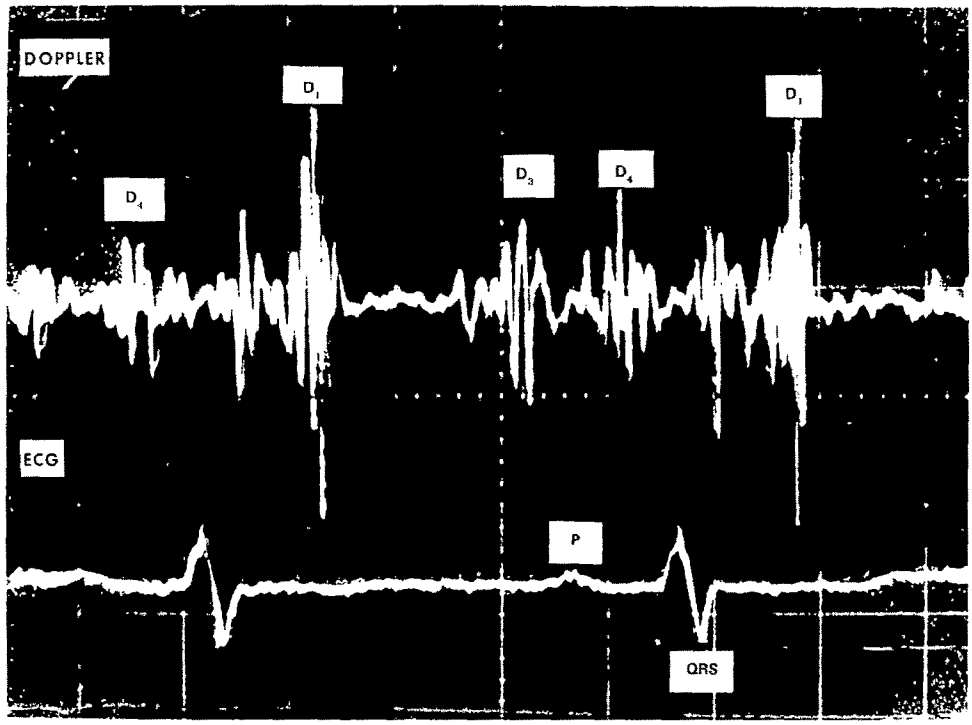


Fig. 1. Oscilloscope photograph of Dopper and ECG from the fetal heart. Three components are clearly seen. One immediately precedes the QRS and is synchronous with the fetal P *(D4)*, most likely representing atrial contraction. Another immediately follows the QRS *(D1)*, most likely representing the closure of the A-V valves. A third *(D3)* appears before atrial contraction, most likely representing A-V valve opening. *D4* and *D1* remain constantly related to each other. *D3* is almost constantly related to *D1* and thus appears more centered as the rate slows. As the rate slows it may confuse Doppler counting circuits which do not account for this component.

the development and validation of an external Doppler FHR monitor designed to provide results approaching the accuracy of the FHR by ECG.

After this system was developed a study was designed to test the accuracy and reliability of the FHR data on high-risk patients admitted in labor at the New York Hospital–Cornell Medical Center. These patients were monitored in the clinical environment as part of their usual care. Previous publications report only visual observation of simultaneous Doppler FHR and scalp ECG FHR, without rigorous analysis of the accuracy.[13, 14] This report describes the computer comparison of the FHR produced by Doppler with that produced by simultaneously obtained fetal scalp ECG.

Development of the Doppler ultrasonic FHR monitor

Distinct Doppler ultrasound (DUS) signals are obtainable from virtually all fetuses after the second trimester, and are easily obtainable from almost all patients in labor, rendering them particularly suitable for monitoring FHR.[15–17] Several commercial monitors utilize the DUS principle but they may show the distressing inability to record tachycardias of over 160 to 180 b.p.m., and a peculiar tendency to count at double the FHR at lower rates (especially rates of 90 b.p.m.).[10] When the signal becomes weak, as during contraction, a false deceleration or indication of artifact (e.g., pen-lift) may occur. The records may be marked by prolonged periods of unphysiologic "jitter" and unphysiologic baseline variability. In general they are regarded and promoted as screening instruments used to decide when to resort to internal methods.[13]

The physiologic properties of the Doppler signal were explored to help understand these problems. The over-all philosophy was to design a Doppler system which would be easy to use, would provide a fetal heart motion Doppler signal of adequate strength and clarity for automatic counting, and which would largely exclude Doppler from other moving structures. The system should also allow for relative lateral motion of transducer and fetal heart. A system was designed which would enhance ultrasonic reflections from certain distances from the transducer and reduce those from others, in essence accepting the ultrasonic reflections from a plane parallel to the abdomen. This

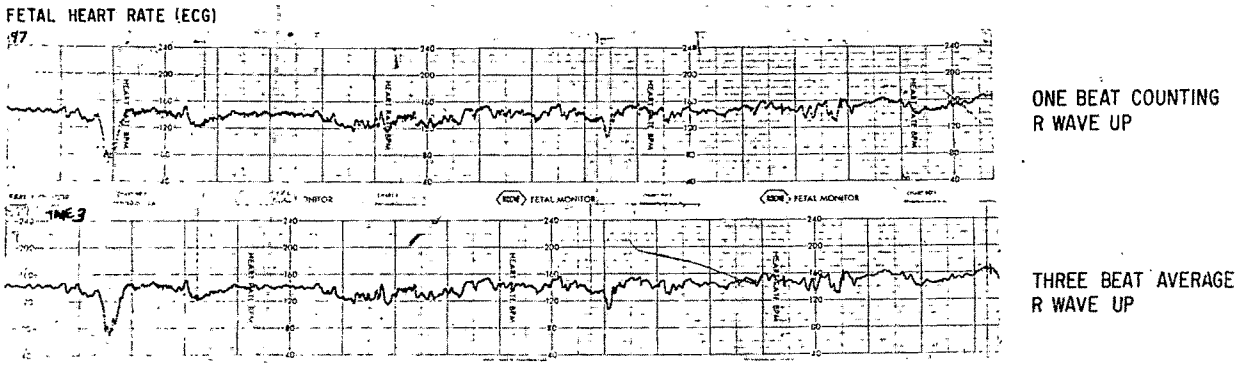


Fig. 2. Comparability of beat-to-beat vs. three-beat average for FHR display. The variability patterns on the FHR display are composed of the sum of the "beat-to-beat" changes of up to 15 to 20 heart beats. Ultrasonic records tend to show increasing apparent, but artifactual, beat-to-beat change ("jitter") with decreasing signal amplitude, this "jitter" tending to totally obscure the long-term variability patterns. Three-beat averaging destroys the "jitter" and retains the variability. This illustration shows there is essentially no visible difference between a FHR processed by beat-to-beat or three-beat average, even with the ECG.

would allow the operator to "range in" on the best sounding fetal heart Doppler to optimize signal clarity. This "depth ranging" capability is accomplished by superimposing a digital code on the transmitted 2 megaHertz continuous ultrasonic wave and awaiting return of the code. As the ultrasonic propagation time through tissue is known, the expected time from various distances is known. By the use of correlation techniques, the system accepts only ultrasonic reflections at the distances selected by the operator. The correlation technique also enhances the selected reflection threefold and reduces reflections from other distances by 30-fold. By selecting the depth which produces the loudest, clearest, fetal heart Doppler, all returns from this area are so enhanced and other Doppler sources are largely excluded. The correlation also allows use of lower power because of the electronic signal enhancement.

Continuous wave ultrasound allows lower power (<5 mw. per square centimeter) and the use of less expensive, more reliable electronics than pulsed Doppler. A 2 MHz frequency is used because it largely excludes detection of blood flow, and it provides adequate tissue penetration at lower power with adequate resolution (0.25 mm.). (Tissue penetration is inversely proportional to ultrasonic frequency and resolution is directly proportional.)

After preliminary investigation[18] a research system capable of detecting returned Doppler reflection from 0 to 1,000 Hz was constructed,* as this was the domain which seemed to contain almost all the reasonable energy reflection. The Doppler reflections of the fetal heart would necessarily include those from the slowest and fastest moving components. However, an automatic counting system requires the most distinct signals with a reasonable amount of energy (highest signal-to-noise ratio).

Doppler signals were tape recorded* from this system from a series of about 100 labor and prenatal patients. When available, simultaneous scalp or abdominal ECG's were recorded. These data were explored with ultrasonic spectrographs and various types of filtering. The region of highest signal-to-noise was found between 100 and 500 Hz. The heart produced the largest amount of energy below 100 Hz, but the signal was not distinct. Fetal motion and transducer motion also produced their greatest amount of energy below 100 Hz. Little usable signal was obtained over 500 Hz.

The Doppler in the frequency range of interest contained three primary components at lower FHR (<~140 b.p.m.) and two primary components at higher FHR (Fig. 1). At lower rates one component appeared after the P, representing atrial contractions, a second appeared after the QRS, representing A-V valve closing, and aortic opening, and a third appeared a consistent time after the second, representing A-V valve opening. These components have been studied and documented in adults and fetuses.[19, 20] At higher FHR, diastole is infringed upon and the opening of the valves is produced by atrial contraction. The two remaining sounds produce the heart-sound–like tones of

*Ranging System RA5—Roche Medical Electronics Inc., Cranbury, New Jersey.

*Hewlett-Packard Instrumentation Recorder, Model 3960, Hewlett-Packard Inc., Waltham, Massachusetts.

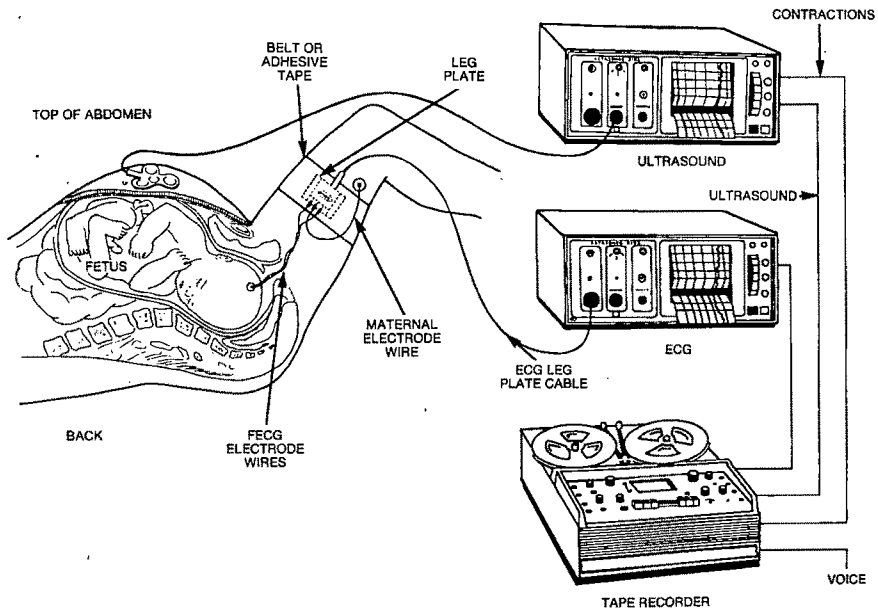


Fig. 3. Data collection for the computer study of accuracy of Doppler FHR. A series of high-risk patients in ordinary clinical care were monitored by simultaneous Doppler ultrasound and fetal scalp ECG methods. The strip charts were kept for analysis and the signals (Doppler, ECG, contractions) were tape recorded for replay into other instruments and subsequent computer analysis of resultant FHR's.

Doppler systems. At lower FHR the "gallop rhythm–like" sounds of the three components can be clearly heard. At a FHR of about 90 b.p.m., the A-V opening signal is midway between the two atrial contractions. Thus centrally placed components may be interpreted by monitors as another heart beat, causing a sudden doubling of the FHR. Both between and during contractions, for no apparent reason, but probably due to fetal motion, the Doppler signal might markedly diminish in amplitude. If the monitor could not follow these changes rapidly enough, more and more infrequent beats were counted, producing an apparent, but false, deceleration. The predominant component changed from time to time, probably because of change of fetal position. At times this would occur suddenly and produce a new complex, but often the changes were cyclic. This might produce spurious beat-to-beat changes if the system were to shift from one component to another as they cyclically changed.

These data clearly indicated possible solutions. The ultrasonic spectrographs and filter data were used to choose a Doppler domain where the signal-to-noise is optimized and fetal motion, abdominal motion Doppler, and maternal arterial Doppler are minimized. The system adapts to the changes in number of components to avoid counting the A-V valve opening as another beat during bradycardia, and further adapts to follow tachycardias. The system adapts rapidly to changes in signal amplitude. It contains a short-term memory to help determine where a potentially weak signal might be and focus the systems attention at this point. This circuit also helps the system lock onto one Doppler component and not shift until another becomes clearly predominant, helping to prevent spurious beat-to-beat "jitter."

The low-signal false-deceleration problem was also approached by finding the weakest DUS signal reliably countable and barring data display if the signal dropped below this level for at least 5 seconds. For this system, this level is eight to 40 times smaller than typical DUS in labor and has a signal-to-background amplitude of about 1.5 to 1.

Further study of DUS beat-to-beat FHR display showed apparent but artifactual beat-to-beat changes ("jitter") as the Doppler weakened because the signal became less distinct and thus it was more difficult to trigger on the exact same point with each beat. A running three-beat average of the heart rate (in beats per minute) allowed retention of underlying variability patterns and prevented their destruction by the "jitter" of weakening signal. In no way does this change the variability patterns, as they are usually composed of over 10 heart beats (Fig. 2).

The causes of false artifact indication were studied by playing tape-recorded DUS data into a fetal monitor, designed to circumvent the above problems.

Table I. Clinical data and record evaluation

Case No.	*Indications for monitoring*	*Monitoring abnormalities*	*Total time U/S monitoring*	*Outcome*	*Doppler FHR record evaluation*
Computer-analyzed cases:					
E-1	1. Poor progress of labor 2. Cephalopelvic disproportion 3. Meconium	Occasional small, early decelerations	2 hr., 24 min.	Cesarean section, Apgar 9, 10	90% usable Doppler FHR
E-5 (Fig. 4)	1. Premature rupture of membranes 2. Pitocin induction 3. Meconium	Severe variable decelerations	2 hr.	Cesarean section, nuchal cord, Apgar 3, 10	100% usable Doppler FHR
E-7 (Fig. 5)	1. Pre-eclampsia 2. Primigravida 3. Age 32 4. Pitocin induction 5. Failure to progress	None	3½ hr.	Cesarean section, Apgar 6, 8	85% usable Doppler FHR
E-13	1. Cephalopelvic disproportion 2. Meconium staining	Variable decelerations, long periods of bradycardia	3 hr.	Cesarean section, Apgar 9, 10	90% usable Doppler FHR
E-15	1. Post maturity 2. Prostaglandin E_2 induction	None	11 hr., 40 min.	3,260 Gm. fetus, Apgar 9, 10	98% usable Doppler FHR
E-37	1. Postmaturity 2. Induction 3. Failure to progress	Rare shallow decelerations	10 hr.	Cesarean section, meconium, cord around neck, Apgar 7 at 5 min.	96% usable Doppler FHR
E-38 (Fig. 6)	1. Premature rupture of membranes 2. Induction 3. Relative CPD 4. Failure to progress	Rare variable decelerations	10½ hr.	Cesarean section, Apgar 9, 10	95% usable Doppler FHR
E-41	1. Gravida 4 2. Previous cesarean Sections ×2 3. Previous colostomy 4. Poor prenatal care 5. Anemia—hematocrit 29% 6. Oxytocin induction	Rare variable decelerations	45 min.	Low outlet forceps, light meconium-stained fluid, Apgar 9, 10	Only 30 min. of record available for review; 85% usable Doppler FHR
M. C.	Rh Negative	Rare decelerations	75 min.	Apgar 9, 10	91% usable Doppler FHR
S. J.	1. Pre-eclampsia 2. Meconium 3. Cephalopelvic disproportion 4. Failure to progress	Rare variables	1½ hr.	Cesarean section, 3,380 Gm. female, Apgar 7, 9	96% usable Doppler FHR
M. N.	Postmaturity	Accelerations to 190 b.p.m.	8 hr., 20 min.	Apgar 9, 10	90% usable Doppler FHR

The resultant phases were entered into a computer,* which computed the FHR for each interval as well as the beat-to-beat change between intervals. The predominant component varied from time to time and the counting circuits might suddenly shift to a newly predominant component, producing an apparent, but artifactual, sudden "beat-to-beat" change. This change was responsible for many "artifact indications" (pen-lift) and "jitter" for no apparent reason.

These studies also showed the beat-to-beat changes to be quite small, usually less than 5 b.p.m. Even in the

*PDP 11/45, Digital Equipment Corp., Maynard, Massachusetts.

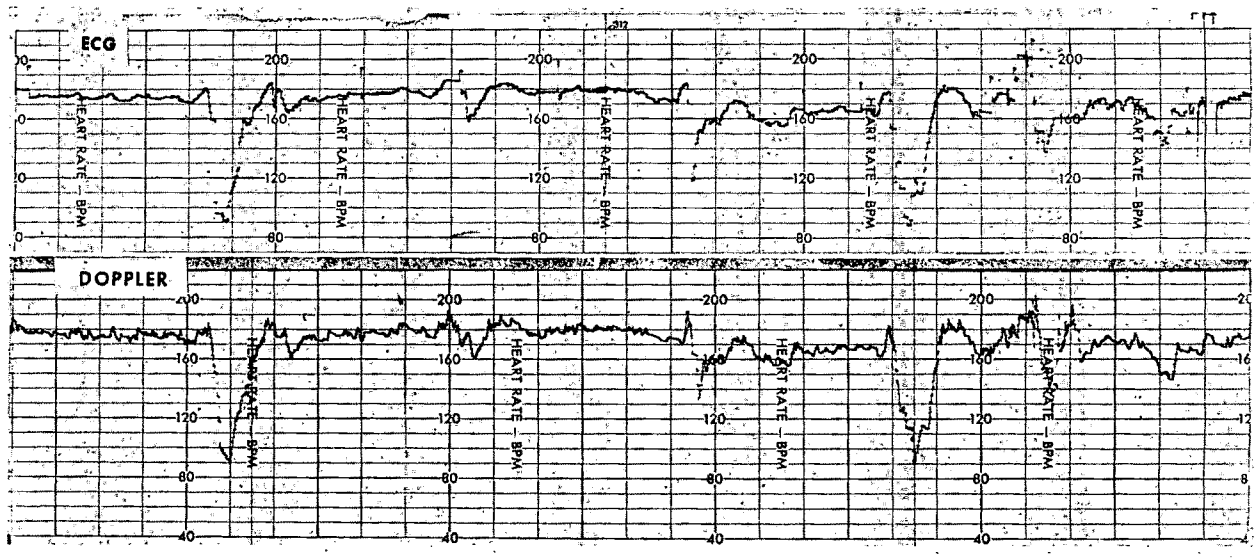


Fig. 4. Simultaneous beat-to-beat ECG and Doppler FHR records showing accurate representation of variable decelerations. The upper record is derived from beat-to-beat ECG, the lower from Doppler. Rates from 90 to 180 b.p.m. are well represented. Severe decelerations and tachycardia are well followed by the Doppler-derived FHR.

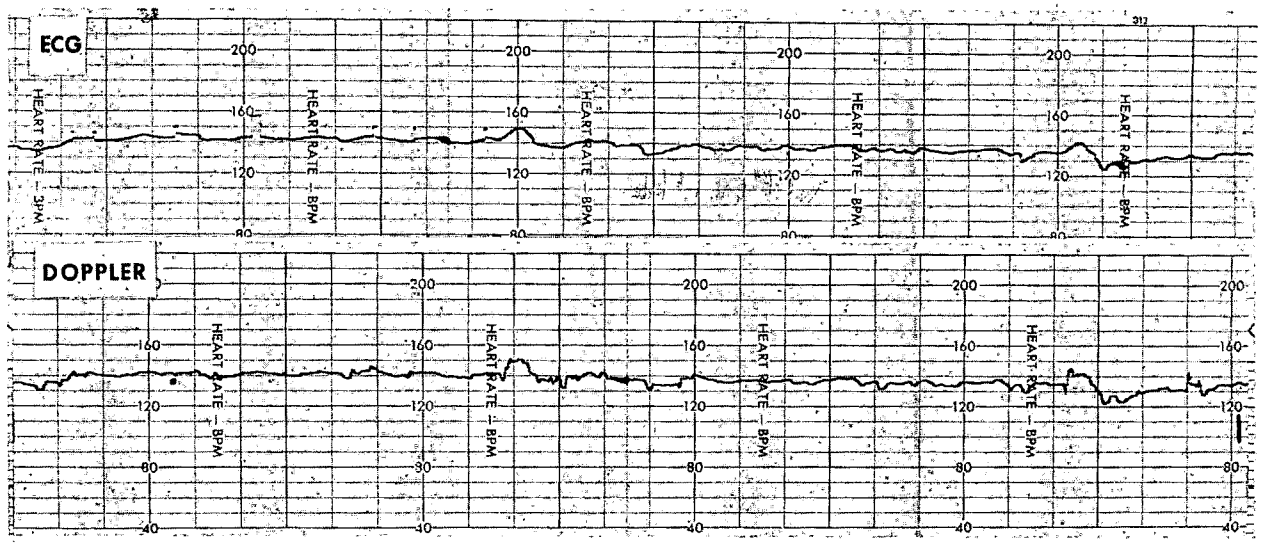


Fig. 5. Simultaneous beat-to-beat ECG and Doppler FHR showing limited variability in both. This pre-eclamptic patient in labor was treated with large doses of $MgSO_4$. The beat-to-beat ECG FHR (top) shows loss of variability, well represented by the Doppler-derived FHR (bottom).

steepest variable deceleration, it rarely exceeded 10 b.p.m. Periods of severe interference with fetal Doppler from excessive fetal or patient motion, or moving the transducer, were characterized by many sequential beat-to-beat changes of at least 25 b.p.m. Serial changes of 25 b.p.m. or more were chosen as representing unphysiologic data, with the recognition that they might represent arrhythmias.

A circuit was added to check for discrepancies of over 25 b.p.m. in beat-to-beat FHR changes.

The system allows for up to two sequential changes of 25 b.p.m. before it indicates the data are erratic (because each skip produced at least one long and one short interval). During this time the last valid FHR is displayed. If subsequent intervals are out of the physiologic range, the system bars display of the information because it was most likely derived from interference rather than fetal heart Doppler. In order to prevent attempts at restarting on erratic data and the resulting "jitter" and "splatter," the system was re-

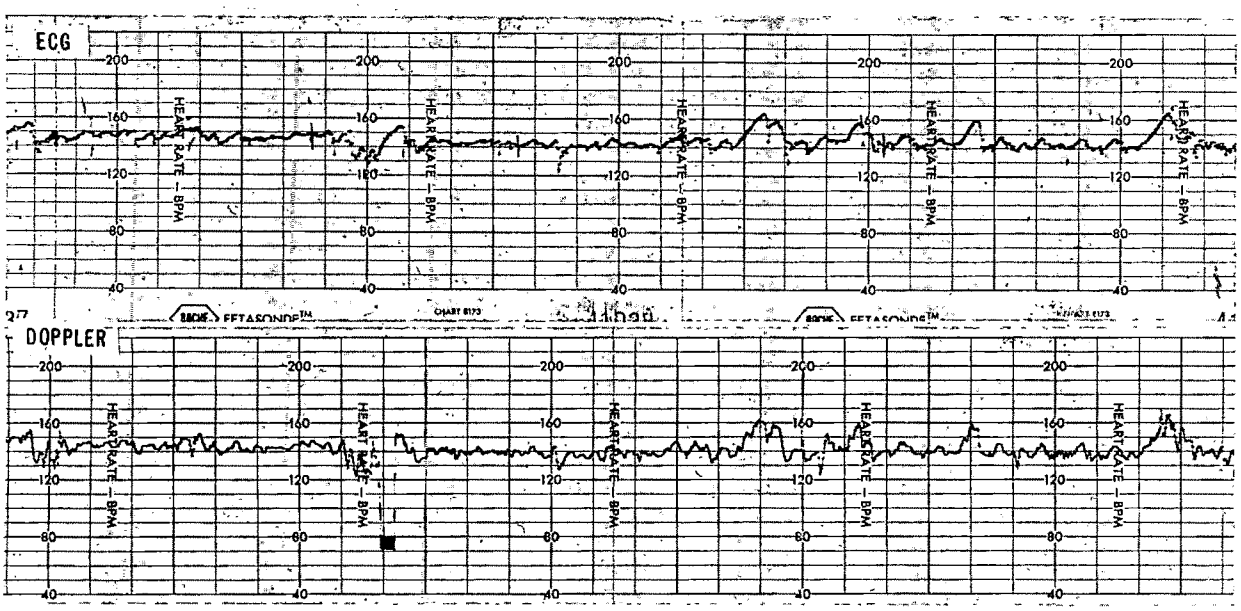


Fig. 6. Simultaneous beat-to-beat ECG and Doppler FHR showing accurate reproduction of variability patterns and accelerations. The variability patterns and accelerations shown in the ECG FHR record (top) is closely approximated by the Doppler FHR record (bottom). The short black bar on the Doppler record indicates an area where the system could not produce an accurate FHR and automatically barred any data from showing, rather than display false data. This area would not have been included in the computer comparison.

quired to have 4.5 seconds of reasonable FHR before it would remove the bar to observation. Theoretically, a system which allows holding for two erratic beats might be holding for half the time; however, this metastable state was not observed to occur—the fetal Doppler either was usable or not.

The transducer proved a key element in system performance. It allows coverage of a circular area of up to 10 cm. diameter at the level of the fetal heart to allow for normal fetal descent and some skin-fetal displacement without loss of DUS. This is to minimize the need for replacing the transducer. It was made flexible so the crystals would not lift from the skin during the change in abdominal shape occurring during contraction, to help eliminate the problem of losing the Doppler during normal spontaneous uterine contractions.

Circuits were designed and packaged to test whether these problems were indeed solved in clinical use. After extensive bench testing with tape-recorded data, clinical studies were performed.

Materials and methods

In addition to continuous observation of performance on a large series of patients, a rigorous analysis was undertaken. This analysis is the substance of this report. After appropriate consent, simultaneous recordings of Doppler ultrasound and ECG were obtained on a series of 12 high-risk patients. In nine, the Doppler and ECG were tape recorded from the time the internal electrode was applied until delivery (Fig. 3).

The strip charts were analyzed for total time of DUS monitoring and per cent of usable (nonartifactual) Doppler FHR data (Table I) and the visual impression of correlation of the records was recorded.

The tape-recorded signals were played into two new commercial fetal monitors.* If several magnetic tapes were available for a patient, a typical one was used to conserve computer time. The electrical levels which control the FHR recorder were entered into the analogue-to-digital converter of a computer. The two resultant FHR levels were each sampled at 250 ms. intervals with 10 bit accuracy (0.18 b.p.m.). This sampling rate was selected to provide accurate description of variability patterns. According to communications theory, a continuous repetitive sinusoidal curve may be described by sampling at twice the frequency. In practice, four to eight times is adequate for nonsinusoidal curves, and in this study the ratio is over 10 times the frequency of the variability patterns. (Sampling rate frequency 4 Hz; variability frequency 0.1 to 0.2 Hz.) At each sample, the FHR for each was

*Fetasonde 2102, Roche Medical Electronics Inc., Cranbury, New Jersey.

Table II. Doppler-ECG FHR computer comparison, results

Case No.	Record description	Computer time (min.)	Avg. FHR by ECG (b.p.m.)	Mean difference			Standard deviation of differences				
				Control	Study		Control		Study		
				b.p.m.	b.p.m.	FHR (%)	b.p.m.	FHR (%)	b.p.m.	FHR (%)	Control/study ratio (%)
E-1	Accelerations	70	138	0.2	−0.9	0.6	4.3	3.1	10.3	7.4	58
E-5	Severe variable decelerations, baseline tachycardia to 190 b.p.m.	26	167	1.9	0.5	0.3	6.2	3.7	12.6	7.5	49
E-7	Normal—minimal variability	60	133	−1.2	−0.6	0.5	3.8	2.9	4.0	3.0	95
E-13	Variable decelerations	46	153	0.2	<0.2	0.1	3.5	2.3	10.0	6.5	35
E-15	Poor ECG record	21	153	−0.5	−1.16	0.8	12.8	8.4	14.1	9.2	91
E-37	Rare variable decelerations	50	149	−0.6	−0.3	0.2	7.6	5.1	6.7	4.5	113
E-38	Normal	62	143	−0.4	−1.5	1.0	4.8	3.4	10.4	7.0	46
E-41	Rare variable decelerations	27	135	−0.4	−0.6	0.4	3.3	2.4	10.6	7.8	31
Averages		45		−0.1	−0.3	0.5	5.8	3.9	9.8	6.6	65
Total		362									

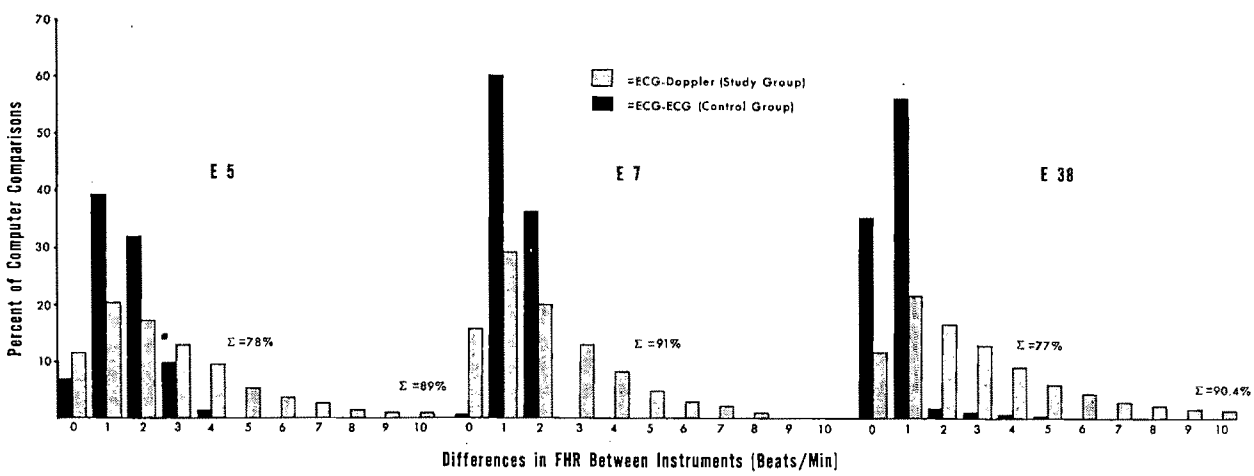


Fig. 7. Typical distribution of differences of paired measures between control (ECG-ECG) and study (ECG-Doppler) FHR's. The great majority of the control differences are 0 to 2 b.p.m. The great majority of the study differences are 0 to 5 b.p.m. The E values indicate the per cent of study differences with 5 and 10 b.p.m. The control differences account for a substantial part of the study differences. The differences fall off rapidly and quickly assume negligible proportions. Note that *E 5* is one of the statistically poorer cases over all, yet the distribution is little different from that of *E 7*, one of the statistically best cases.

calculated and the difference was calculated and stored. After completion of the tape the computer printed the average, range, and standard deviation of the FHR, and the number of samples for each instrument, as well as the average difference between instruments, the S.D. of the differences, and the distribution of the differences.

When "artifact" was determined by the Doppler system, no comparisons were performed until 4 seconds later. This allowed entry of some spurious ECG data and some spurious Doppler data as the system entered the artifact mode.

Two computer studies were performed: (1) *control (ECG-ECG):* The ECG was entered simultaneously into

Per cent of differences in FHR measurement in given ranges					
In 5 b.p.m.			*In 10 b.p.m.*		
Control (%)	*Study (%)*	*Study/control ratio (%)*	*Control (%)*	*Study (%)*	*Study/control ratio (%)*
97	76	78	98	91	93
90	78	87	92	89	97
99	91	92	99	97	98
98	73	74	98	89	91
87	79	91	91	89	98
97	86	89	98	96	98
95	86	90	98	96	98
98	80	82	99	93	94
95	81	85	97	93	96

both instruments to determine differences between instruments and form a basis for comparison of beat-to-beat ECG and Doppler FHR, and (2) *study (ECG-Doppler):* the ECG was entered into one instrument and Doppler into the second. Beat-to-beat ECG FHR was compared to Doppler FHR.

Results

The clinical data and usability are summarized in Table I. One patient with a poor ECG due to poor electrode placement could not be studied by computer and is not listed in Table I. All patients had risk factors. Four had totally normal records and two had severe pathology. Monitoring by Doppler ranged from about 45 minutes to almost 12 hours. The data were at least 85 per cent usable in all cases and, of the 11 remaining records, the average amount of usable FHR per patient was 93 per cent.

Visual comparison showed excellent agreement of FHR periodic patterns. FHR's of 60 to 200 b.p.m. were recorded. No instances of half or double counting were noted even in the steepest deceleration or tachycardia (Figs. 4 to 6).

Tape recordings of data were available from eight patients for computer analysis. Data were analyzed from 21 to 70 minutes per patient, for a total of 362 minutes for the eight patients (Table II). The mean difference in FHR of the study group (Doppler vs. ECG) ranged from 0.2 to 1.5 b.p.m., all less than 1 per cent of the average FHR. The mean differences of the control group had similar values, indicating that these average differences represent only interinstrument differences.

The control standard deviation (S.D.) of the differences is 3.9 per cent of the average FHR. The study group's S.D. averages 6.6 per cent, but in one case (E-37), it is lower than the control. On the average, the ratio of S.D. control/S.D. study is 65 per cent. This ratio is an attempt to compare the S.D. of the study to an "invariant" control. Since S.D. includes occasional spurious artifactual values, the distribution of differences is more meaningful. For this study, differences of 5 b.p.m. or less and 10 b.p.m. or less were chosen as they were considered clinically insignificant because they are not visible except on close inspection, and they are well within recommended recorder accuracy (±3 per cent of full scale, an allowable difference of up to 15 b.p.m.). The distributions show that on the average, 81 per cent of Doppler FHR values are within 5 b.p.m. of ECG beat-to-beat FHR and 93 per cent are within 10 b.p.m. The respective control values are 95 and 97 per cent. The ratio of study to control (a measure to compare to an "invariant" control) shows an average of 85 per cent approach of Doppler FHR to beat-to-beat ECG FHR within 5 b.p.m. and an average of 96 per cent within 10 b.p.m. (Figs. 7 and 8). The Doppler artifact system seems to effectively bar false data presentation, as the remaining 85 to 100 per cent of the data closely approximate the ECG-derived FHR.

Since introduction of this new external system the utilization of fetal monitoring has risen from 25 per cent of patients in labor to approximately 75 per cent.

Comment

While routine monitoring by Doppler ultrasound has previously been discussed,[13, 22] its accuracy has not been reported in a rigorous fashion. This study shows the exploration and solution of problems hindering acceptance of ultrasonic FHR monitoring. Both visual observation of records and computer analysis document that the Doppler-derived FHR from this new instrument follows clinical periodic patterns, accurately reproduces long-term variability, and approaches closely the numerical values of the fetal scalp ECG-derived beat-to-beat FHR. Qualitatively the records are often not identifiable as to source signal, if presented as unknowns.

The control study of the differences show that two typical instruments are highly reproducible; the average difference of the control study was within the accuracy of the computer measurements. The instru-

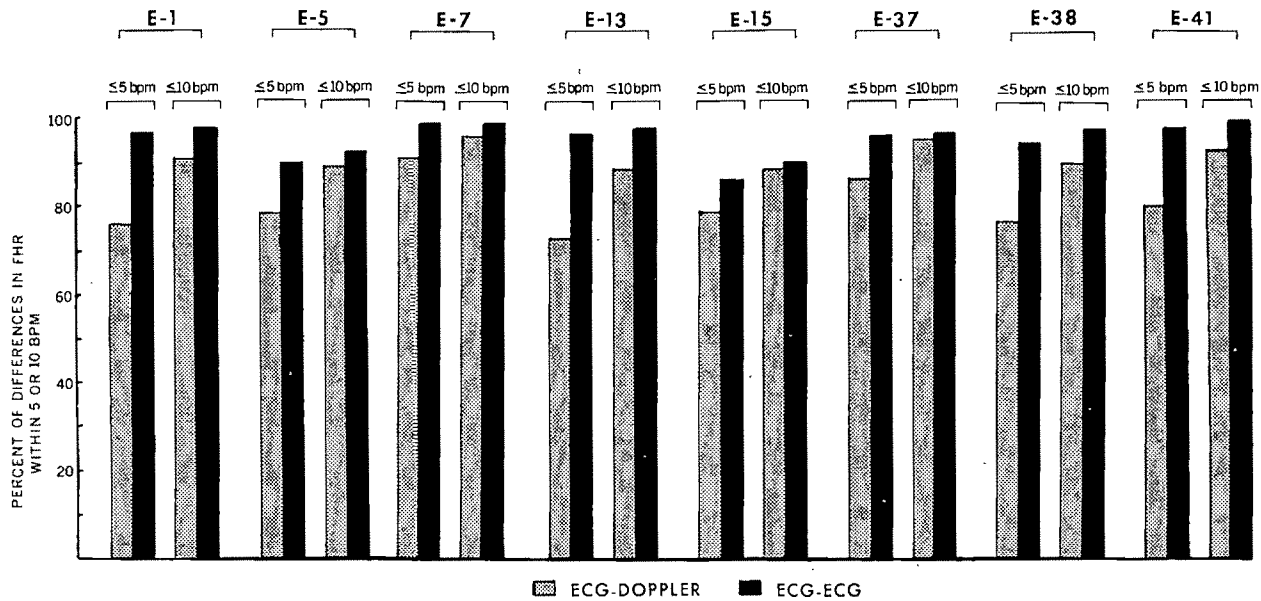


Fig. 8. Doppler FHR accuracy. For each patient, the per cent of measurements showing ≤ 5 b.p.m. difference and ≤ 10 b.p.m. difference are represented for control (black) and study (stippled) measures. The number of study measurements within the ≤ 10 b.p.m. difference closely approaches the control value. This limit is within clinically acceptable bounds. The study values also approach the control values in the ≤ 5 b.p.m. group.

ment is equipped with a "1 per cent cardiotach," but it should be appreciated that this refers to the accuracy of measurement between the pulses generated by the detection of the R waves. The ECG itself is often not detectable with 1 per cent reproducibility when it is of low voltage and/or there is a high level of background interference due to loose electrodes or maternal agitation.

In contrast to a previous report,[13] the baseline variability is usually closely approximated, and the record often appears almost identical to an internal record. The utilization of Doppler in 93 per cent of monitored patients and the availability of at least 85 per cent of usable data in over 90 per cent of patients in the study is higher than previously given by Shenker,[22] who reported that 296/1000 (30 per cent) of patients were monitored externally and 49/296 (17 per cent) were monitored by both. No mention was made of per cent of usable data or the quantitative aspects.

In this study transducer replacements were typically required three times during the course of labor, thus reducing the attention needed for the monitor. This compares favorably with the frequent need to replace several spiral electrodes during the course of labor, particularly if single spirals are used.

These data, and the experience that the Doppler is relied upon in the great majority of cases, show it to be a clinically useful tool, making external FHR monitoring practical, accurate, and meaningful.

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Adrenocorticotropic hormone in human fetal blood at delivery

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Adrenocorticotropic hormone (ACTH) concentrations in umbilical arterial and venous plasma were measured in newborn infants delivered both vaginally and by cesarean section. Mean ACTH was significantly higher in the arterial (602.0 pg. per milliliter) than venous (261.5 pg. per milliliter) plasma in vaginal deliveries ($p < 0.01$). Arterial plasma of babies born by elective cesarean section before initiation of labor contained less ACTH (384.7 pg. per milliliter) when compared to those delivered after labor had started (698.7 pg. per milliliter). Serial determinations of ACTH in pooled fetal blood obtained during labor showed that the average hormone titers increased significantly from first stage (295.2 pg. per milliliter) to second stage of labor (440.5 pg. per milliliter), and reached a peak at delivery (645.4 pg. per milliliter). The pituitary gland of the fetus at midtrimester contained ACTH. Possible mechanisms for fetal secretion of ACTH at delivery are discussed.

THE ESTROGEN levels in the cord blood and maternal urine are elevated following adrenocorticotropic hormone (ACTH) injection to the fetus in utero, whereas they are markedly depressed after dexamethasone injection.[1] With micromethods, estriol, dehydroepiandrosterone (DHA), 16α-hydroxy-DHA, and cortisol in fetal scalp blood increase during the course of delivery.[2, 3] These data suggest that the pituitary adrenal function of the human fetus has a probable effect upon the production of estriol precursor(s), such as DHA and/or 16α-hydroxy-DHA, during pregnancy. It was postulated that the fetal hypophyseal adrenal axis plays an important endocrinologic role during the enormous environmental changes and the stresses of delivery.[3, 13] The following clinical study was undertaken to investigate fetal ACTH production during delivery and to attempt to correlate ACTH with steroid hormone secretion.

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Material and methods

All patients were seen in the Department of Obstetrics and Gynecology of the Teikyo University Hospital. Six women underwent elective cesarean section before the onset of labor for cephalopelvic disproportion and a further six patients were sectioned for fetal salvage after a prolonged labor of over 30 hours. The umbilical cord was clamped by two forceps immediately following delivery of the infant; the proximal site close to the umbilicus and the distal site near the placenta. Blood samples were obtained from the umbilical arteries and veins with separate heparinized syringes. Umbilical blood samples were collected in a similar way from 12 primiparas immediately after normal vaginal deliveries. Fetal blood samples were collected from the scalp of 18 fetuses during labor according to the method of Saling.[4] It was not possible to do ACTH determinations on the small volumes of plasma obtained with individual scalp blood samples. Therefore, three individual plasma samples collected at identical stages of labor were pooled. The umbilical blood samples of those cases were also pooled in the same manner as the scalp blood; each plasma sample collected from a given individual case being adjusted to the same volume. The patients were informed about the study and gave their consent; there were no problems with any of the mothers or the infants. Radioimmunoassay of ACTH was performed on the

Table I. ACTH concentrations in the cord blood of babies delivered vaginally

Source of samples	*No. of infants*	*ACTH concentrations* (pg./ml. ± S.E.) (range)*
Umbilical artery	12	602.0 ± 106.4 (196.6 – 1592.0)
Umbilical vein	12	261.5 ± 34.7 (64.4 – 467.9)

*The difference between arterial and venous concentrations is statistically significant ($p < 0.01$).

six groups of pooled samples. The heparinized blood samples were centrifuged immediately at 3,000 r.p.m. for 15 minutes at 4° C. The plasma was separated and kept at −20° C until assayed.

A 10 mg. amount of silicic acid was added to each milliliter of plasma in a stoppered glass centrifuge tube, shaken for 20 minutes, and centrifuged at 3,000 r.p.m. for 10 minutes. After the supernatant had been discarded, the silicic acid precipitate was washed with 5 per cent horse plasma in water and the washing solution was discarded. Then 250 μl of a mixture of glacial acetic acid, acetone, and water (1:25:100) were added to the precipitate, mixed for 10 minutes, and separated by centrifugation at 3,000 r.p.m. for 10 minutes.[5] The supernatant was transferred to assay tubes and evaporated by a stream of nitrogen in a water bath kept at 50° C. The residue was dissolved in 0.1 ml. of the standard diluent and was subjected to radioimmunoassay. The standard diluent consisted of 0.5 per cent human serum albumin, 0.5 per cent mercaptoethanol, and 500 U. Trasylol per milliliter in 0.075M phosphate saline buffer, pH 7.4. Synthetic ACTH standards were made up in horse plasma and were extracted in exactly the same way as plasma samples. The synthetic human ACTH standard was a gift of Dr. Noboru Yanaihara, Shizuoka, Japan. The antihuman ACTH serum, Wellcome Reagents, LTD., England, was diluted to 1:10,000 with the standard diluent, and 0.1 ml. was added to the assay tube containing extracts of the standard or sample. The radioiodination procedure of ACTH was performed with ^{125}I by the modified method of Greenwood and associates.[6] Following purification on a Bio-gel P-10 column, the iodinated ACTH was diluted with the standard diluent and the radioactivity in each milliliter was set to about 15,000 c.p.m. Then 0.1 ml. of this solution was added to the assay tube, mixed well, and incubated at 4° C. for 3 days. The separation of antibody bound and unbound ACTH was effected by adding 0.2 ml. of a suspension of dextran-coated charcoal.[7] After centrifugation the supernatants were transfered to separate tubes, and the charcoal precipitate and supernatant were counted in an Aloka Auto-well Gammer System.

Pituitary glands of the fetuses removed for therapeutic abortions in the midtrimester were homogenized in 0.01N HCl and centrifuged in the cold, and the supernatant was diluted with the standard diluent. ACTH in the pituitary extract at various dilutions was assayed.

The following substances were checked for cross-reactivity in the ACTH radioimmunoassay: LER 907, hLH, hFSH, prolactin, synthetic oxytocin, vasopressin, synthetic LH-RH, HCG, and prostaglandins (F_2 and E_2).

Recovery experiments were carried out with 100 pg. of standard ACTH added to horse plasma.

Results

Specificity of the ACTH radioimmunoassay system. The binding capacity of the antiserum was 48 per cent under the present experimental conditions, and it was possible to measure ACTH that ranged from 10 to 640 pg. per assay tube. Among the nine compounds tested, none demonstrated cross-reactivity when 1 to 9 ng. were assayed.

Recovery and blank of the assay. Recoveries of 100 pg. of ACTH added to 1 ml. of horse plasma were 89.4 ± 25.3 per cent. Extracts of blank plasma samples showed values close to zero.

ACTH levels in cord blood. The average values of 12 normal vaginal deliveries are shown in Table I. The mean ACTH concentration of the umbilical artery blood was 602.0 pg. per milliliter (range, 196.6 to 1,592.0 pg. per milliliter) and that of the vein was 261.5 pg. per milliliter (range, 64.4 to 467.9); the difference was statistically significant ($p < 0.01$). This trend was not found in babies delivered by elective cesarean section before the onset of labor; the average ACTH levels in the umbilical artery and vein were 384.7 pg. per milliliter (range, 187.5 to 992.0) and 333.0 (range, 67.9 to 912.0), respectively, and were not statistically different. The ACTH levels in the umbilical blood vessels were increased if cesarean section was performed after labor had begun; the mean arterial value was 698.7 pg. per milliliter (range, 255.0 to 1,176.0) as compared to the average vein concentration of 487.6

Table II. ACTH concentrations in the cord blood of babies delivered by cesarean section before and after the onset of labor

	Timings of cesarean section			
	Before labor		*After labor*	
Sources of samples	*No. of cases*	*ACTH* (pg./ml. ± S.E.) (range)*	*No. of cases*	*ACTH* (pg./ml. ± S.E.) (range)*
Umbilical artery	6	384.7 ± 129.2 (187.5 – 992.0)	6	698.7 ± 132.0 (255.0 – 1176.0)
Umbilical vein	6	333.0 ± 122.0 (67.9 – 912.0)	6	487.6 ± 126.7 (58.9 – 960.0)

*None of the differences is significant.

Table III. ACTH concentrations in pooled fetal blood collected from the scalp and the umbilical vessels during the course of delivery.

		*ACTH**	
Source of samples	*No. of groups*	*Pg./ml. ± S.E. (range)*	*Per cent*
Fetal scalp:			
First stage of labor	6	295.2 ± 133.0 (54.4 – 622.0)	100.0
Second stage of labor	6	440.5 ± 143.7 (109.9 – 1,000.0)	144.6†
Cord blood at delivery:			
Umbilical artery	6	645.4 ± 202.4 (214.0 – 1,592.0)	247.5‡
Umbilical vein	6	300.2 ± 71.6 (88.2 – 583.8)	137.0

*The increments as compared to the first stage value are statistically significant († $p < 0.05$, ‡ $p < 0.01$).

Table IV. ACTH contents in the fetal pituitary gland at midtrimester

		ACTH	
Weeks of gestation	*No. of cases*	*Ng./pituitary ± S.E. (range)*	*Ng./mg. tissue ± S.E. (range)*
16-20	23	16.08 ± 1.98 (3.6 – 38.8)	2.01 ± 0.34 (0.44 ± 5.71)

pg. per milliliter (range, 58.9 to 960.0), though the difference was not significant (Table II).

ACTH in fetal blood during labor. The average ACTH levels of the fetuses during delivery as measured in the pooled samples at identical stages are shown in Table III. In the first stage of labor, the mean value was 295.2 pg. per milliliter (range, 54.4 to 622.0). During the second stage of labor the average titer of ACTH was 440.5 pg. per milliliter (range, 109.9 to 1,000.0); this value was 44.6 per cent greater than that of the titer for the first stage samples and the increment was statistically significant ($p < 0.05$). At delivery of the same cases, the ACTH concentration in the umbilical artery was 645.4 pg. per milliliter (range, 214.0 to 1,592.0); 147.5 per cent more than the comparable fetal titer in the first stage of labor ($p < 0.01$). The ACTH titer in the umbilical vein blood obtained at delivery was 300.2 pg. per milliliter (range, 88.2 to 583.8). This was similar to the hormone concentrations found at the first stage of labor.

ACTH in the fetal pituitary gland. The average ACTH content in 23 anterior pituitary glands of fetuses at midtrimester was 2.01 ng. per milligram (range, 0.44 to 5.71) of wet tissue weight (Table IV). The extracts of the anterior hypophysis showed a parallel curve with standard ACTH when serial dilutions of the extract were made and assayed.

Comment

In an earlier study utilizing a radioimmunoassay technique, Berson and Yallow[8] reported that plasma ACTH concentrations were significantly higher in the cord blood (161 ± 29 pg. per milliliter, mean and S.D.) than the maternal venous blood. Similar results were

reported by Allen and associates[9] (mean, 226 pg. per milliliter) and Miyakawa and associates[10] (261.98 ± 81.65 pg. per milliliter, mean and S.D.), who emphasized the fact that ACTH did not cross the placental barrier. Those investigators also suggested that ACTH might be secreted by the fetus. Winters and associates[17] showed the absence of elevated ACTH levels in the cord blood of infants born after spontaneous labor (143 ± 7 pg. per milliliter, mean value for term infants at delivery). The absolute values of ACTH reported in the present communication are higher than those of other investigators, probably due to different sampling techniques or to the assay method in which an extraction loss is considered. In experimental animals, the pituitary adrenal relationship in fetal life is well established; decapitation of fetuses in utero resulted in marked atrophy of the adrenal gland.[11] Our results demonstrate that ACTH concentration was significantly higher in the blood from umbilical arteries than from umbilical veins in normal vaginal deliveries. The onset of labor seemed to alter ACTH levels in the fetus. It may be postulated from these results that ACTH is actively secreted in the fetus and that the rate of its secretion is augmented by the stress of labor.

In sampling the cord blood, a larger amount of blood is easily collected from the vein than the arteries. Previous reports on ACTH concentration in the cord blood represent the hormone levels in the mixed cord blood, the greater part of which might have consisted of blood returned from the placenta.[8–10, 17] A relatively low ACTH level in the umbilical vein blood may partly, if not entirely, be due to the effect of aminopeptidase of the placenta.[12] In order to further investigate the effect of labor upon the ACTH secretion in the fetus, serial samples were obtained from fetuses, plasma was pooled, and ACTH levels were determined. Since ACTH does not cross the placental barrier, the fetus actively secretes ACTH during the course of delivery with increasing titers as delivery nears. The increasing concentrations of ACTH could be related to uterine contraction, variations in oxygen, the trauma of delivery, or result from other causes. A possibility must also be considered that the samples obtained by Saling's technique had less ACTH because the samples were collected in glass capillaries. One may also postulate that the fetal pituitary secretes ACTH in reponse to the tremendous environmental changes occurring in delivery. To our knowledge this is the first report to demonstrate that the ACTH concentration in fetal blood significantly increases as labor progresses.

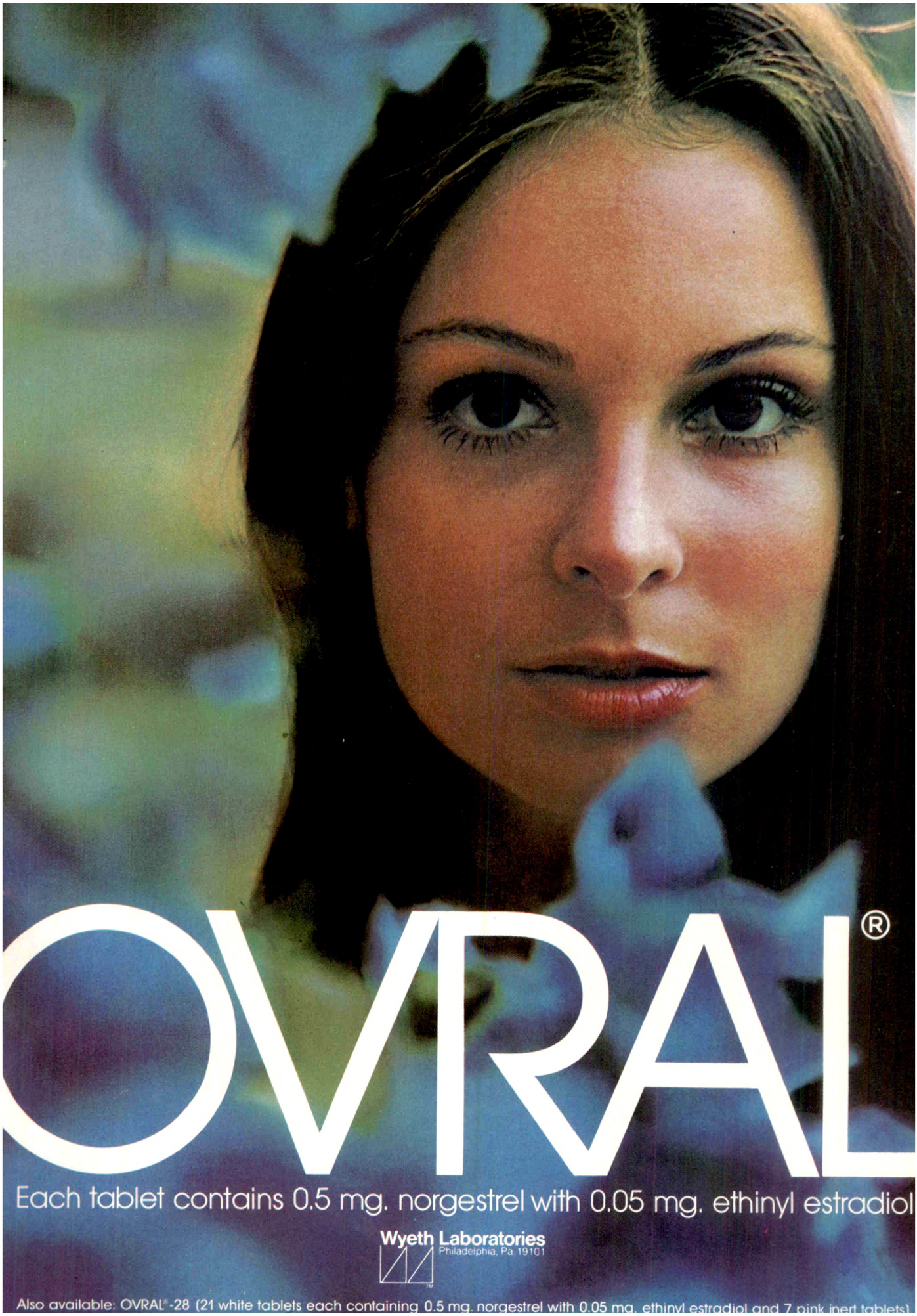
We have previously demonstrated that the fetal blood levels of estrogen, dehydroepiandrosterone, 16αOH-dehydroepiandrosterone, and cortisol tended to increase during the course of delivery.[2, 3] Fetal cortisol levels at term are reported elsewhere[13, 14] and correlate with the present sutdy. Although the contents were lower when compared to the adult pituitary,[16] radioimmunoreactive ACTH was found in the fetal pituitary at midtrimester. Previous[1, 13, 15] and present studies add further evidence to the theory that the fetal pituitary adrenal axis is functioning during delivery and steroid output is increased responding to the secretion of fetal ACTH. However, as already suggested, hormonal changes in fetal blood might be the result of labor and the hormones studied may not trigger the onset of labor.

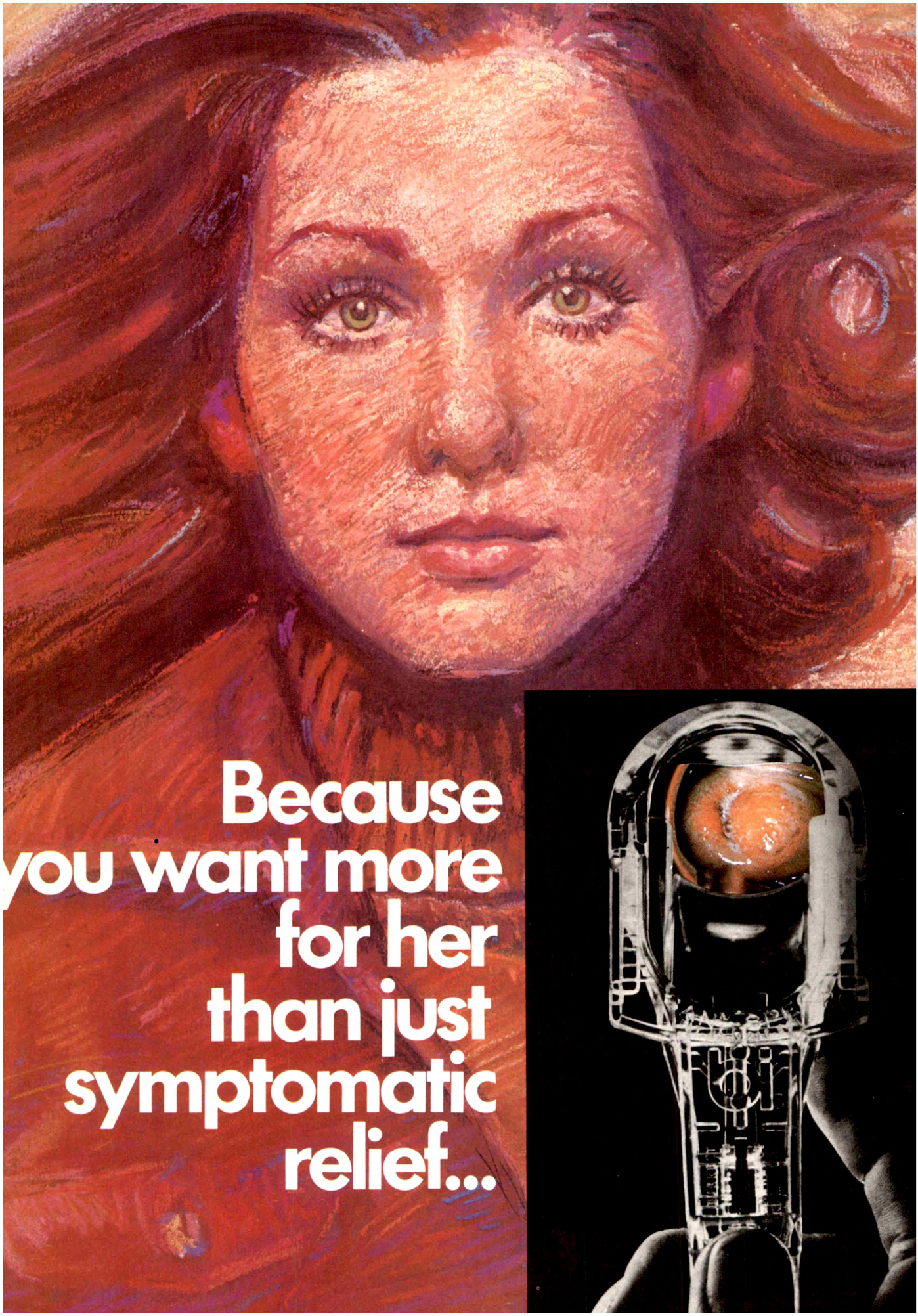
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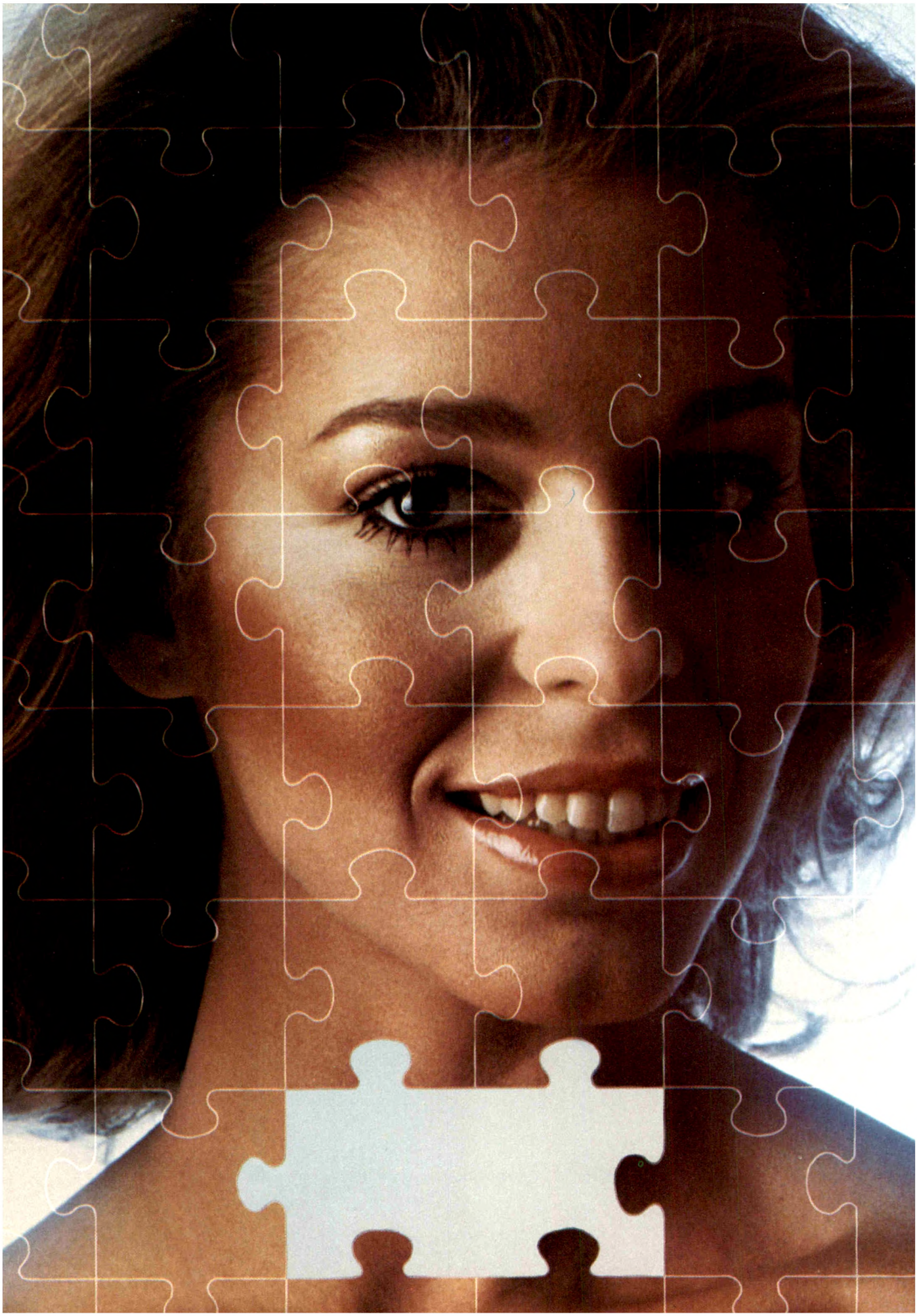
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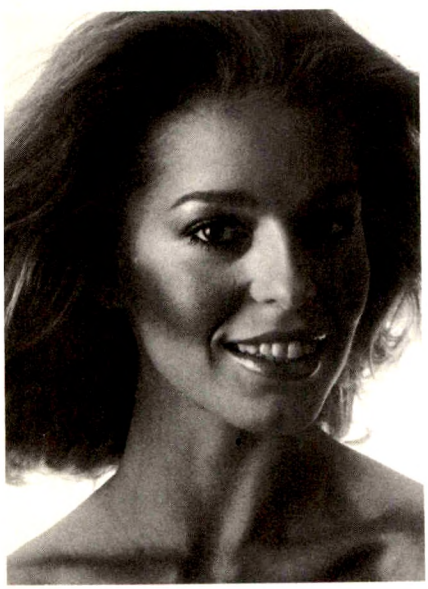
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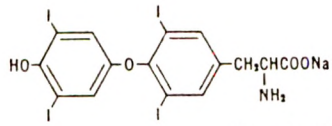
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Indications: SYNTHROID (sodium levothyroxine) products serve as specific replacement therapy for reduced or absent thyroid function of any etiology. SYNTHROID **Injection** can be used intravenously whenever a rapid onset of effect is critical, and either intravenously or intramuscularly in hypothyroid patients whenever the oral route is precluded for long periods of time.

Contraindications: There are no absolute contraindications to SYNTHROID (sodium levothyroxine) therapy. Relative contraindications include acute myocardial infarction, uncorrected adrenal insufficiency and thyrotoxicosis. (See WARNINGS)

Warnings: Patients with cardiovascular diseases warrant particularly close attention during the restoration of normal thyroid function by any thyroid drug. In such cases, low initial dosage increased slowly by small increments is indicated. Occasionally, the cardiovascular capacity of the patient is so compromised that the metabolic demands of the normal thyroid state cannot be met. Clinical judgment will then dictate either a less-than-complete restoration of thyroid status or reduction in thyroid dosage.

Endocrine disorders such as diabetes mellitus, adrenal insufficiency (Addison's disease), hypopituitarism and diabetes insipidus are characterized by signs and symptoms which may be diminished in severity or obscured by hypothyroidism. SYNTHROID (sodium levothyroxine) therapy for such patients may aggravate the intensity of previously obscured symptoms and require appropriate adjustment of therapeutic measures directed at these concomitant disorders.

Thyroid replacement may potentiate the effects of anticoagulants. Patients on anticoagulant therapy should have frequent prothrombin determinations when instituting thyroid replacement to gauge the need to reduce anticoagulant dosage.

Precautions: Overdosage with any thyroid drug may produce the signs and symptoms of thyrotoxicosis, but resistance to such factitious thyrotoxicosis is the general rule. With SYNTHROID (sodium levothyroxine) **Tablets,** the relatively slow onset of action minimizes the risk of overdose but close observation in the weeks following institution of a dosage regimen is advised. Treatment of thyroid hyperactivity induced by oral medication is confined to interruption of therapy for a week, followed by reinstitution of daily therapy at an appropriately reduced dosage.

Adverse reactions: Adverse reactions are due to overdose and are those of induced hyperthyroidism.

Dosage and administration: For most adults, a final dosage of 100 mcg (0.1 mg) to 200 mcg (0.2 mg) of SYNTHROID (sodium levothyroxine) **Tablets** daily will restore normal thyroid function and only occasionally will patients require larger doses. Failure to respond adequately to a daily oral intake of 400 mcg (0.4 mg) or more is rare and should prompt reconsideration of the diagnosis of hypothyroidism, special investigation of the patient in terms of malabsorption of L-thyroxine from the gastrointestinal tract or poor adherence to therapy.

The concomitant appearance of other diseases, especially cardiovascular diseases, usually dictates a replacement regimen with initial doses smaller than 100 mcg/day (0.1 mg).

In otherwise healthy adults with relatively recent onset of hypothyroidism, full replacement dose of 150 mcg (0.15 mg) or 200 mcg (0.2 mg) has been instituted immediately without untoward effect and with good therapeutic response. General experience, however, favors a more cautious approach in view of the possible presence of subclinical disorders of the cardiovascular system or endocrinopathies.

The age and general physical condition of the patient as well as the severity and duration of hypothyroid symptoms determine the starting dosage and the rate of incremental dosage increase leading to a final maintenance dosage. In the elderly patient with long standing disease, evidence of myxedematous infiltration and symptomatic, functional or electrocardiographic evidence of cardiovascular dysfunction, the starting dose may be as little as 25 mcg (0.025 mg) per day. Further incremental increases of 25 mcg (0.025 mg) per day may be instituted at three to four week intervals depending on patient response. Conversely, otherwise healthy adults may be started at higher daily dosage and raised to the full replacement dosage in two to three weeks. Clearly it is the physician's judgment of the severity of the disease and close observation of patient response which determines the rate of dosage titration.

Laboratory tests to monitor thyroid replacement therapy are of limited value. Although measurement of normal blood levels of thyroxine in patients on replacement regimens frequently coincides with the clinical impression of normal thyroid status, higher than normal levels on oral replacement of levothyroxine occasionally occur and should not be considered evidence of overdosage per se.

In all cases, clinical impression of the well-being of the patient takes precedence over laboratory determination in determining the appropriate individual dosage.

In infants and children, there is a great urgency to achieve full thyroid replacement because of the critical importance of thyroid hormone in sustaining growth and maturation. Despite the smaller body size, the dosage needed to sustain a full rate of growth, development and general thriving is higher in the child than in the adult, as much as 300 mcg (0.3 mg) to 400 mcg (0.4 mg) per day.

In myxedema coma or stupor, without concomitant severe heart disease, 200 to 500 mcg of SYNTHROID **Injection** may be administered intravenously as a solution containing 100 mcg/ml. Although the patient may show evidence of increased responsivity within six to eight hours, full therapeutic effect may not be evident until the following day. An additional 100 to 300 mcg or more may be given on the second day if evidence of significant and progressive improvement has not occurred. Like the oral dosage form, SYNTHROID **Injection** produces a predictable increase in the circulating level of hormone with a long half-time. This usually precludes the need for multiple injections but continued daily administration of lesser amounts intravenously should be maintained until the patient is fully capable of accepting a daily oral dose.

In the presence of concomitant heart disease, the sudden administration of such large doses of L-thyroxine intravenously is clearly not without its cardiovascular risks. Under such circumstances, intravenous therapy should not be undertaken without weighing the alternative risks of the myxedema coma and the cardiovascular disease. Clinical judgment in this situation may dictate smaller intravenous doses of levothyroxine.

SYNTHROID **Injection** by intravenous or intramuscular routes can be substituted for the oral dosage form when ingestion of SYNTHROID **Tablets** is precluded for long periods of time.

How Supplied: SYNTHROID (sodium levothyroxine) **Tablets** are supplied as scored, color-coded compressed tablets in 6 concentrations: 25 mcg (0.025 mg)—orange . . . 50 mcg (0.05 mg)—white . . . 100 mcg (0.1 mg)—yellow . . . 150 mcg (0.15 mg)—blue . . . 200 mcg (0.2 mg)—pink . . . 300 mcg (0.3 mg)—green.

SYNTHROID (sodium levothyroxine) for **Injection** is supplied in 10 ml vials containing 500 mcg of lyophilized active ingredient and 10 mg of Mannitol, U.S.P. A separate 5 ml vial containing Sodium Chloride Injection, U.S.P. is provided as a diluent.

Directions for reconstitution: Reconstitute the lyophilized sodium levothyroxine by aseptically adding 5 ml of the Sodium Chloride Injection, U.S.P. to the vial. Shake vial to insure complete mixing. **Use immediately** after reconstitution. Discard any unused portion.

U.S. Pat. 2,889,363

January 1975

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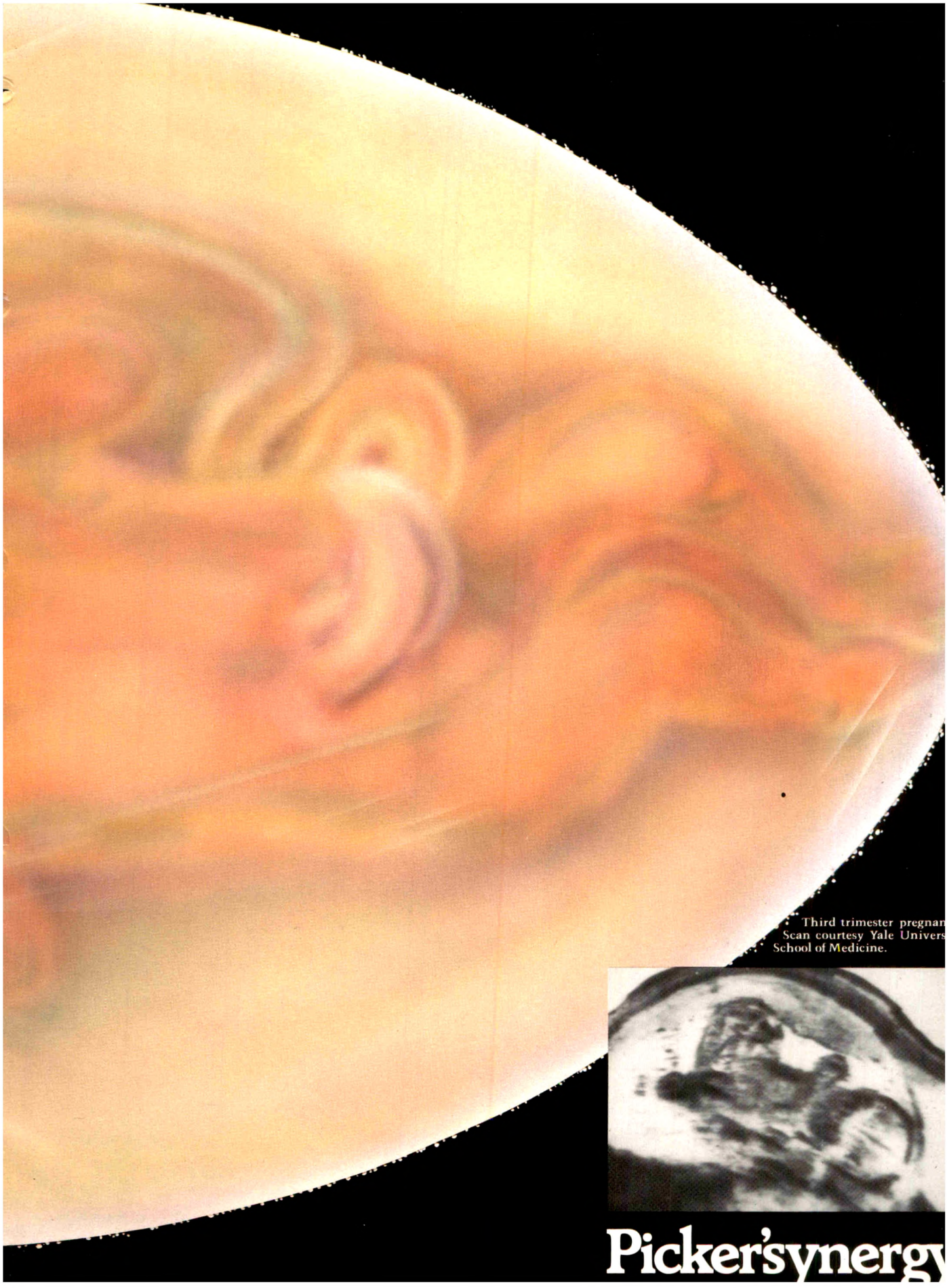
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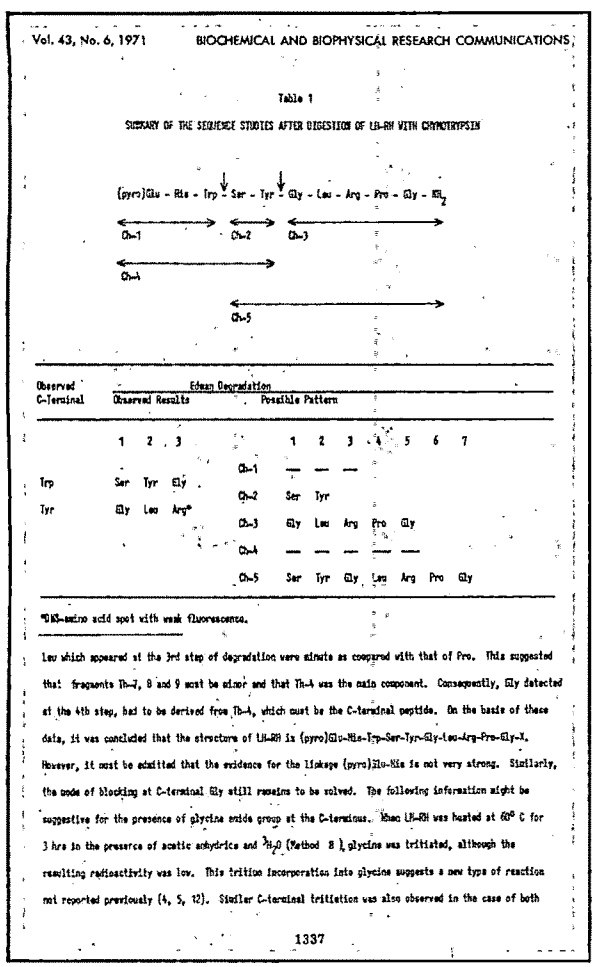
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Structure of the porcine LH- and FSH-releasing hormone. I. The proposed amino acid sequence

HISAYUKI MATSUO, YOSHIHIKO BABA, RAGHAVAN M.G. NAIR, AKIRA ARIMURA, AND ANDREW V. SCHALLY

Biochemical and Biophysical Research Communications, vol. 43, pp. 1334-1339, 1971



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Table 1

SUMMARY OF THE SEQUENCE STUDIES AFTER DIGESTION OF LH-RH WITH CHYMOTRYPSIN

(pyro)Glu - His - Trp - Ser - Tyr - Gly - Leu - Arg - Pro - Gly - NH_2

Ch-1 Ch-2 Ch-3 Ch-4 Ch-5

Observed C-Terminal	Edman Degradation: Observed Results			Possible Pattern						
	1	2	3		1	2	3	4	5	6	7
Trp	Ser	Tyr	Gly	Ch-1	—	—	—				
Tyr	Gly	Leu	Arg*	Ch-2	Ser	Tyr					
				Ch-3	Gly	Leu	Arg	Pro	Gly		
				Ch-4	—	—	—	—	—		
				Ch-5	Ser	Tyr	Gly	Leu	Arg	Pro	Gly

*DNS-amino acid spot with weak fluorescence.

Leu which appeared at the 3rd step of degradation were minute as compared with that of Pro. This suggested that fragments Th-7, 8 and 9 must be minor and that Th-4 was the main component. Consequently, Gly detected at the 4th step, had to be derived from Th-4, which must be the C-terminal peptide. On the basis of these data, it was concluded that the structure of LH-RH is (pyro)Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-X. However, it must be admitted that the evidence for the linkage (pyro)Glu-His is not very strong. Similarly, the mode of blocking at C-terminal Gly still remains to be solved. The following information might be suggestive for the presence of glycine amide group at the C-terminus. When LH-RH was heated at 60° C for 3 hrs in the presence of acetic anhydride and ^3H_2O (Method B), glycine was tritiated, although the resulting radioactivity was low. This tritium incorporation into glycine suggests a new type of reaction not reported previously (4, 5, 12). Similar C-terminal tritiation was also observed in the case of both

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Schally and his colleagues of New Orleans were the first to successfully isolate the hypothalamic releasing hormone for luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Several of their earlier papers reported various aspects of this monumental research. For instance, isolation of pure luteinizing hormone–releasing hormone (LH-RH) with description of its biological and chemical properties appeared two months previously (Biochem. Biophys. Res. Commun. 43: 393, 1971); however, tryptophan was not mentioned in the amino acid composition which was obtained by acid hydrolysis. The correct amino acid sequence of the LH (and FSH)–releasing decapeptide appeared in this report (see Table 1, at left). These papers reported for the first time that pure LH-RH stimulates the release of FSH by direct action on the pituitary both in vivo and in vitro. The concept of one hypothalamic hormone regulating the release of both LH and FSH, which to date has not been disproved, also was based on this study. Subsequently, Schally and co-workers synthesized LH-RH (Biochem. Biophys. Res. Commun. 45: 822, 1971). Within a few months, this work was reported independently by R. Guillemin and his colleagues (Biochem. Biophys. Res. Commun. 44: 205, 1971). This research made possible extensive clinical testing of LH-releasing hormone. These developments may promote new approaches to problems of infertility and population control.

Some notes on the background of the isolation, determination of structure, synthesis, and early clinical trials of the luteinizing hormone– and follicle-stimulating hormone–releasing hormone

ANDREW V. SCHALLY

New Orleans, Louisiana

SOME KEY EVENTS paved the way for our group to isolate, determine the structure of, synthesize, and carry out clinical trials of the hypothalamic hormone controlling the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. I have been asked to recount some of these events. The first was the formulation by Green and Harris[1] of the basic theories relating to the hypothalamic control of gonadotropin secretion by the pituitary gland. These theories were supported by anatomic and physiologic evidence. In parallel studies, Sawyer and colleagues[2] demonstrated an involvement of the central nervous system in the control of gonadotropin secretion. However, direct evidence for the existence of a specific hypothalamic chemotransmitter controlling release of LH and FSH or, indeed, of any hypothalamic regulatory hormone was lacking. It was at this stage of the problem (in 1954) that my own involvement began when I was working in the Department of Psychiatry of McGill University in Montreal. Although I was then only an undergraduate, it was my privilege to work closely with Murray Saffran in the friendly fraternal atmosphere of his laboratory. I was also greatly helped by the close comradeship and encouragement of Dr. Robert A. Cleghorn, the Chief of the Laboratory for Experimental Therapeutics in the Allan Memorial Institute of Psychiatry. That period really marked the beginning of my interest in the relationship between brain function and endocrine activity. At that time, several theories existed on the control of secretion of adrenocorticotropic hormone (ACTH), but Murray and I thought that the theory of Green and Harris[1] explained most of the experimental facts. They postulated that neurohumors, which might originate in the median eminence of the hypothalamus and penetrate to the anterior lobe through the portal system, could be responsible for the control of anterior lobe secretion. Murray and I sought to provide evidence for this theory by demonstrating for the first time a direct effect of hypothalamic substances on the pituitary. Encouraged by the success of the in vitro assay system for ACTH based on the use of quartered adrenal glands,[3] we devised a test system for measuring pituitary secretion of ACTH with the use of isolated pituitary fragments.[4] This simple in vitro system proved to be of decisive importance not only for demonstrating the existence of hypothalamic substances controlling the release of ACTH but also (after small modifications) in subsequent investigations of hypothalamic hormones regulating the secretion of thyroid-stimulating hormone (TSH), LH, FSH, growth hormone, prolactin, and melanocyte-stimulating hormone (MSH). Murray and I were able to prove that hypothalamic (and, surprisingly, also neurohypophyseal) tissue contained a substance which stimulated the release of ACTH.[4, 5] We named the substance corticotropin-releasing factor (CRF). Our finding was the first direct proof of the existence of hypothalamic hormones. Murray could have taken all the credit for this important discovery himself since I was then only an undergraduate (and only later a graduate student with him), but he generously shared it with me. I shall always be grateful for this, which helped launch my career in the field. At that time, bonds of mutual respect and friendship between Murray and myself were formed, and they have persisted firmly ever since.

However, despite our initial success, enthusiasm for our work among other endocrinologists did not last very long. CRF activity proved to be very difficult to purify, partly because of its instability and partly

From the Endocrine and Polypeptide Laboratories, Veterans Administration Hospital, and the Department of Medicine, Tulane University School of Medicine.

This paper was received from Dr. A. V. Schally in response to a query concerning the discovery of the luteinizing hormone–releasing hormone structure.

because of the complexity of the assays and interference by substances such as vasopressin and ACTH present in the extracts. Despite agonizing efforts, we were unable to isolate enough material in a pure state for the determination of its structure.

These efforts were started with Murray Saffran in Montreal and continued with Guillemin in Houston, Texas, where I moved in September, 1957, having obtained my doctorate at McGill in May of that year. My years in Houston were discouraging because of serious problems with isolation of CRF and because of my relationship with Guillemin. Our failure to identify CRF cast doubt on the initial findings. We were exposed to sarcasm, skepticism, and even ridicule and contempt by many scientists and physicians in the endocrine field who seemed not to understand the technological problems involved in the effort. CRF and other hypothalamic hormones were called (even in writing) watery illusions, the monster of Loch Ness, and the Abominable Snowman of the Himalayas. I refrain from listing the references; some of the authors of these statements are now actively working with the hypothalamic hormones. Despite these years of frustration, I remained confident that we were right in assuming the existence of hypothalamic hormones regulating anterior pituitary function. Moreover, we were making headway: Methods were being developed for purification, as well as for in vivo assays, and arrangements were made for procurement of the hundreds of thousands of hypothalami of domestic animals necessary for any realistic effort to purify useful quantities of hypothalamic hormones. After my move to New Orleans, Oscar Mayer and Co. was especially helpful and generous to us in that respect. It was also encouraging that some men had the foresight to appreciate the possible scientific and medical importance and diagnostic and therapeutic potential of hypothalamic hormones, if such existed. When Dr. Joe Meyer, the head of Veterans Administration basic research, offered in June, 1962, to set up a Veterans Administration laboratory devoted to research on the hypothalamus and make me its chief, I quickly accepted, despite my feeling that a move would temporarily slow down the progress I was making. For various reasons, among which were the enthusiastic support of Dr. E. H. (Manny) Bresler, then Associate Chief of Staff for Research of the New Orleans Veterans Administration Hospital, Dr. George Burch, then Chairman of the Department of Medicine of Tulane University School of Medicine, and Dr. C. Y. Bowers, the head of the Tulane Endocrine Clinic, and my preference for a southern warm climate where I can continue my daily outdoor swimming, I decided to locate in New Orleans in December of 1962. At that time, I was appointed Associate Professor of Medicine at Tulane and, in 1966, Professor. After a year and a half in provisional laboratories, we moved in 1964 to a new building which was well equipped by the Veterans Administration. Immediately, we began to work with great enthusiasm on all the hypothalamic hormones controlling anterior pituitary function, as well as on hypothalamic lipid-mobilizing substances. The earliest members of our 1962 team were Tommie W. Redding and Weldon H. Carter. They have stayed with me all these years, and without their devoted help we could not have solved the thyrotropin-releasing hormone (TRH) problem in 1969 and the luteinizing hormone–releasing hormone (LH-RH) problem in 1971. Working in a medical environment, I became more aware of patient needs and of materials desirable for better diagnosis and treatment than I had been when in a more academic setting. As my position in New Orleans entailed many research responsibilities, I was greatly helped by the experience acquired in my early years of research (1950 to 1952) at the National Institute of Medical Research, Mill Hill, London, where I was fortunate to work with or be exposed to the stimulating influences of such scientists as Dr. D. F. Elliott, Sir Charles Harington, Dr. Rodney R. Porter, Dr. A. J. P. Martin, Dr. R. Pitt-Rivers, Dr. Jack Gross, Dr. T. S. Work, and many others. These years of instruction were indeed decisive in providing the necessary training and greatly influenced the course of my research career. In my position in New Orleans, I was also able to travel and establish contact with many leading United States scientists and physicians, among them: C. S. (Tom) Sawyer, A. Albert, R. Greep, P. Munson, L. Craig, V. du Vigneaud, S. Segal, Ed Tyler, A. Paulsen, K. Hoffman, and C. H. Li, and foreign ones such as: G. W. Harris, B. A. Houssay, R. Luft, E. Jorpes, J. Porath, A. Tiselius, R. Courrier, R. Hall, C. Gual, A. Zarate, D. Gonzales-Barcena, R. Mancini, L. Martini, J. Zanartu, L. C. Povoa, A. Campos da Paz, J. Botella-Lluisia, and V. Pozuelo. I was actively encouraged and helped by these remarkable men.

Aware of the problem of infertility, on the one hand, and the need, on the other hand, to somehow stem the population explosion, I broadened my interest in the brain and endocrine function to include reproduction and birth control. In fact, the possibility of central inhibition and stimulation of fertility became my main interest after 1962. It had been demonstrated by S. M. (Don) McCann and associates[6] and independently by Campbell and associates[7] that an LH-releasing activity existed in hypothalamic extracts. McCann, in particular, carried out many in vivo studies with crude extracts

to strengthen this evidence.[8] I was able to demonstrate with C. Y. Bowers[9] that purified bovine hypothalamic materials with the properties of peptides stimulate LH release, not only in vivo but also in vitro. The latter was the first demonstration of hypothalamic materials releasing LH by direct action on the anterior pituitary. Soon afterward, my interest in reproductive endocrinology became even deeper, when we confirmed and extended the observations of Igarashi and McCann[10] and Mittler and Meites[11] that hypothalamic materials also release FSH in vivo and in vitro.[12] I was most fortunate that Dr. Akira Arimura, a brilliant physiologist and endocrinologist, joined us in 1965. Because of his knowledge, enthusiasm, research experience, and sheer hard work, Akira made decisive contributions in all phases of our program, which luckily coincided with his own interest. He also broadened our program with many independent contributions and ideas. We continued work on LH-RH and FSH-RH (which at that time we considered as separate entities) and, to broaden our knowledge of reproductive processes at the brain level, we started work on the central effects of contraceptive steroids[13, 14] and clomiphene[15] and on a variety of other projects on reproductive physiology at the central level.[16]

All during this period, we also had been hard at work on TRH. After 1964, we added growth hormone–releasing hormone (GH-RH) and prolactin-release–inhibiting hormone to the list of our research projects. In 1966, we reported[17] that porcine TRH contains three amino acids (glutamic acid, histidine, and proline) in equimolar ratio. This established that TRH was a polypeptide and helped exert a stabilizing influence on a field sorely confused by a proposal that TRH and LH-RH might not be polypeptides.[18, 19] We even persuaded Merck Sharp & Dohme to make eight synthetic analogues of the possible sequence,[16] but, unfortunately, the structure was not correct. As a matter of fact, because of our deep involvement in reproduction and GH-RH, I almost missed solving the TRH problem. However, when Burgus and Guillemin announced at the 1969 Tucson Arizona conference that they also found the same three amino acids in ovine TRH, I realized that we were on the right track on this project. In an attempt to successfully solve the problem, I formed a temporary partnership with Karl Folkers because he had several structural chemists in his laboratory. I provided them with the analogues of TRH made by Merck Sharp & Dohme for structural modifications.[16] Although I consider myself as more of an all-round endocrinologist, or neuroendocrinologist, with a not inconsiderable interest in clinical endocrine research, than a biochemist, I personally carried out the isolation work on TRH and other hormones (see also under LH-RH). Hypothalamic hormones are present in minute amounts and their isolation involves laborious concentration of large amounts of extracts from hypothalamic tissue, so I thought that to get results I would have to do this work myself. I also personally worked on assays and on the determination of structure but did not have sufficient time to elucidate the structures all by myself. Such work in most cases is routine in the peptide field. However, in the case of TRH, we were puzzled by the absence of end groups, although later we established its amino acid sequence in New Orleans.[20] With expert chemical help from Franz Enzmann, Jan Bøler and R. M. G. Nair (in my laboratory), we were able to assign a correct structure to porcine TRH.[21–23] This work was based on the comparison of activity of synthetic analogues of the Glu-His-Pro sequence in assays carried out separately by Cy Bowers and Tom Redding and on physicochemical comparison of these synthetic analogues and natural TRH. However, I like to think that it was really the large number of previous TRH assays carried out by my friend and collaborator Tom Redding on dozens of fractions from the isolation procedures that enabled us to solve the TRH project by helping provide enough material for structural identification of TRH. The credit for completing the TRH project had to be shared with Burgus and Guillemin, who solved the structure of ovine TRH about that time.[24] With TRH out of the way, I terminated my collaboration with Karl Folkers and Cy Bowers.

The solving of the TRH structure made the work on the hypothalamus appear more respectable and removed much of the skepticism surrounding it. Also, we were now able to devote even more of our time to LH-RH and FSH-RH. We established that 11 types of estrogen-progesterone combinations commonly used in contraceptive pills did not suppress the stimulatory effects of LH-RH on the release of LH.[13, 14] From this we postulated that contraceptive steroids act mainly on the hypothalamus. Later, with Drs. Hilliard and Sawyer,[25] and with Dr. Arimura,[26] we were able to prove that these steroids also act on the pituitary gland. This work helped us postulate later that sex steroids may cause differential release of LH and FSH in response to LH-RH/FSH-RH.

At the 1965 Pan-American Congress of Endocrinology in Mexico City, I met Dr. Carlos Gual, then director of the Endocrinology Laboratory of the National Institute of Nutrition in that city. He invited our group to collaborate with him in the clinical testing of hypothalamic hormones in Mexico City. I shall

always remember with gratitude this invitation since it was issued at a time when the hypothalamic hormones were not yet firmly established and also implied confidence on the part of Carlos in our preparations. It was also a great stroke of luck that Dr. Abba J. Kastin joined our group in 1964, mostly to continue his work on MSH and the control of its release. Abba quickly became my best friend and a most efficient collaborator, and, since he was an accomplished clinician, he became responsible for organizing and carrying out most of our clinical studies. In collaboration with Dr. Carlos Gual and Dr. Rees Midgley, we established that highly purified LH-RH unequivocally released LH and FSH in men and women under a variety of conditions.[27, 28] We realized that LH-RH might be useful clinically in contrast to a hypothalamic GH-releasing decapeptide which we isolated in 1969. This encouraged us to continue the vigorous, agonizing effort involved in the isolation of LH-RH. I was able to isolate a small amount (800 μg) of LH-RH from 160,000 hypothalami[29] and obtained proof from work with proteolytic enzymes and amino acid analyses that it is a polypeptide.[30] I passed this LH-RH on to our structural chemists, Drs. Yoshihiko Baba and Hisayuki Matsuo, for degradation work together with suggestions for a structural attack. These suggestions were based on the effect of proteolytic enzymes on LH-RH. Since I did not think that the amounts of LH-RH on hand would be enough to complete our structural work, I continued to work on isolation of additional amounts of LH-RH. As in the case of TRH and the first batch of LH-RH, this involved a great effort, both physical and mental, as well as patience, and experience. There were even some personal risks, for example, when working with 100 L. of diethyl ether daily for several days.[31] In the meantime, Drs. Baba and Matsuo were working desperately hard and were making good headway toward the elucidation of the structure of LH-RH. Dr. Baba was using the Edman-Dansyl procedure and Dr. Matsuo used his own selective titration method for C-terminal analysis which probably was the key for determining the whole structure of LH-RH with the very small amount of material then on hand. We were able to draw unambiguous conclusions about the amino acid sequence and submitted the first paper,[32] after Dr. Arimura found the synthetic decapeptide made in our laboratory and based on the proposed structure of LH-RH to be highly active in releasing LH in vivo. The structure of LH-RH was also quickly confirmed by our using conventional sequential analyses after cleavage of the N-terminal (pyro)glutamyl residue by a special enzyme.[33]

The first paper[32] reporting the correct sequence of LH-RH appeared June 18, at the time of the 1971 meeting of the Endocrine Society in San Francisco, at which I announced the structure, but the journal did not reach the audience. The drama surrounding that presentation was well captured in an article by Graham Chedd.[34] For example, until the last minute, we did not know if Guillemin's group was also going to announce the structure of this very much sought-after molecule. We were quite determined to share in the discovery. I previously decided not to participate in the International Symposium on Gonadotropins held in May at the New York Hospital–Cornell Medical Center, which preceded the San Francisco meeting by a few weeks, in order to be able to continue my experimental work. However, Dr. Arimura was authorized to release the structure of LH-RH at this symposium, should Guillemin or his associates announce it there. They did not, so the drama was reserved for San Francisco. Between March and May, I also gave several lectures at various meetings in the United States and hinted that we might announce the structure at the Meeting of the Endocrine Society in San Francisco. I had a feeling that some members of the audience at these preceding lectures did not quite believe me, but nevertheless the large Imperial Ballroom of the San Francisco Hilton, where I was to give my paper announcing the structure, was very crowded. I listened with excitement and suspense during the immediately preceding lecture and discussions, in which Guillemin's group did not report the isolation, structure, and synthesis of LH-RH; I then rose to my feet and announced them. It was one of the most joyous moments in my life, to announce for the first time the solution to the problem which had fascinated me and others for so long, especially inasmuch as the discovery might have a great scientific, clinical, and even social impact because of the possibilities of stimulation and inhibition of fertility it offers. It should be noted that we won the race to solve the structure of LH-RH with the use of only a small fraction of available hormone. By May, 1971, I was able to isolate over 11 mg. of pure LH-RH,[31] so that the structure could and would have been easily completed in any case by standard conventional methods. But Drs. Baba's and Matsuo's splendid structural analyses[32, 33] on the ultra-micro scale enabled us to achieve our objective about one month earlier, and our big "reserves" were never committed into the race. We vigorously exploited our lead with extensive in vivo and in vitro studies to demonstrate that our decapeptide was indeed the physiologic hormone.[35–38] Since in all these studies natural preparations of LH-RH, as well as synthetic ones, stimulated the release of not only LH

but also FSH, we put forward a concept that one hypothalamic hormone—our decapeptide—controls the secretion of both gonadotropins from the pituitary gland.[39] We tried to explain the occasional preferential release of one or the other gonadotropin by the effect of sex steroids directly on the responsive pituitary tissue.[37] This concept still has not been disproved and, even if another FSH-RH exists, our decapeptide probably still represents the main FSH-RH activity, at least in porcine hypothalamic tissue. In clinical studies, Dr. Kastin and I established an unequivocal lead by carrying out a variety of studies in human beings in association with Dr. Carlos Gual and later Drs. Arturo Zarate, David Gonzalez-Barcena, and Don Schalch, at Hospitals of the Instituto Mexicano de Seguro Social, first using highly purified LH-RH of natural origin and then the synthetic hormone.[27, 28, 37, 40–44] We were also pleased that no adverse side effects of any kind were observed with natural LH-RH or with synthetic LH-RH. We felt that these investigations established the principles of the diagnostic and therapeutic use of LH-RH. Induction of ovulation with LH-RH in collaboration with Dr. Zarate[44, 45] was confirmed and extended by recent studies in Chile with Dr. Zanartu.[46, 47] In male infertility, LH-RH also may find some uses.[48] Of more than 600 publications (counting papers, abstracts, and reviews) our laboratory produced between 1963 and 1974, about half of these were devoted to LH-RH or related reproductive topics. We never would have been able to complete this arduous writing and publishing task without the consistent brilliant editorial help of Dr. William Locke, of the Ochsner Clinic, and occasionally Dr. Ed Ferguson, Jr., and Dr. Manny Bresler, of the Veterans Administration Hospital.

After our announcement of its structure, LH-RH was synthesized in many other laboratories in anticipation of its importance in clinical medicine. The activity of various synthetic materials confirmed the correctness of the structure formulated by us.[43, 44] Basic and clinical studies by others also showed that LH-RH releases LH and FSH in laboratory and domestic animals and human subjects.[43, 49] The hypothalamus suddenly rocketed to the top of the endocrine popularity list. How long it will remain fashionable is difficult to speculate, but the domination of various United States and foreign endocrine meetings by papers on TRH, LH-RH, and GH-RIH has been truly remarkable. Some work even suggests that LH-RH may have an effect on libido,[50] but we believe that such effects, whether exerted directly on the central nervous system (a general idea we proposed with Dr. Kastin) or through the mediation of sex steroids, are still not clearly proved. Other investigators who 15 years ago scoffed at the idea of hypothalamic hormones are now proposing the existence of an astronomical number. Needless to say, we did not agree with their earlier views and we do not agree with their current ones. It is a great tragedy that the untimely death of Geoffrey Harris will not enable him to see the full fruition of his hypothalamic theories. His remarkable insight enabled him to postulate the existence of LH-RH, and before he died, late in 1971, he saw his life's work proved. He was even able to define some of the advances in identification of hypothalamic hormones as "milestones in the history of endocrinology."[51] Harris' death was a great personal loss and left me with a deep sense of grief for many months.

In the meantime, we tried to sustain our momentum in the work on LH-RH with immunologic studies and synthesis of analogues. Immunologic studies by Dr. Arimura in our laboratory and by other groups led to production of antisera to LH-RH and development of a radioimmunoassay (RIA) for LH-RH.[52] We were able to show that such antisera caused gonodal atrophy in male animals and blocked the release of LH and FSH and ovulation in cycling rats, and others confirmed these findings.[52, 53] Perhaps here lies another potential method of birth control. The RIA for LH-RH showed that the peak of serum LH-RH coincides with the surge of LH and that, in fact, LH-RH secretion most probably induces this preovulatory rise in blood LH.[54] The synthesis of various analogues of LH-RH by David and Esther Coy in our laboratory and by others enabled two classes of these compounds to be established: (1) stimulatory, superactive analogues causing prolonged liberation of LH and FSH which should be more practical than LH-RH for ovulation induction in women,[55, 56] and (2) inhibitory analogues which block LH and FSH release and ovulation and which may eventually form the basis of a new contraceptive method.[57–60] Thus, my dream of being able to control reproduction at the central level may one day come true.

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COMMUNICATIONS IN BRIEF

This section is suitable for reporting cases, results of therapeutic trials, and descriptions of new procedures or instruments. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Unilateral tubal twin gestation

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UNILATERAL TUBAL multiple gestation is exceedingly rare as evidenced by the fact that the last authentically reported case was in 1969.[1] Since the first reported case by de Ott[2] in 1891, a number of cases of multiple gestation occurring in one tube have been reported. The most common form of a multiple gestation involving a tube is the combined extrauterine (tubal) and intrauterine gestation. A unilateral twin gestation is more common than bilateral twin tubal gestation. Even more rare is a unilateral tubal triplet gestation followed by an interstitial twin gestation. A single case of a quintuplet tubal gestation has been reported.

Mrs. J. G., a 34-year-old Negro, gravida 3, para 2, was admitted to the Columbia-Presbyterian Medical Center on March 19, 1975, with irregular vaginal bleeding and pelvic pain. The last menstrual period was December 29, 1974. She had excessive intermittent vaginal spotting since that time.

Dilatation and curettage were performed with subsequent microscopic examination revealing decidual reaction. The patient was carefully followed in the outpatient department. She had no pain or vaginal bleeding until April 2, 1975, when she developed lower abdominal pain for which she was readmitted. Pelvic examination revealed a 6 cm. tender right adnexal mass. The vital signs were completely stable. An exploratory laparotomy was performed, and approximately 150 ml. of dark blood was noted in the peritoneal cavity. The medial portion of the right Fallopian tube was markedly dilated and hemorrhagic. A right salpingo-oophorectomy was done. In the midportion of the Fallopian tube, there was a hemorrhagic area which measured 6.0 by 6.5 by 2.5 cm. Upon cutting of the specimen, one amniotic sac was noted. This sac contained two embryos each measuring 1.5 cm. in length. No abnormalities were noted grossly or microscopically.

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Although there have been two reports of dizygotic unilateral tubal twin gestation, it is generally accepted that most cases of unilateral tubal twin gestation have been monozygotic as evidenced by the close correlation of size and developmental stage of the embryos. The case just reported appears to uphold this idea.

The etiologies of tubal multiple gestation appear to be the same as those encountered in singular tubal gestation. These include tubal damage or anatomic alteration from pelvic inflammatory disease, congenital abnormalities, tumors, and surgical intervention. A strong family history for twins is not always found, although the patient in the case just presented had had stillborn twins.

The preoperative diagnosis of unilateral multiple gestation is exceedingly difficult to make. A history suggestive of possible multiple gestation with an adnexal mass disproportionately large compared to the duration of amenorrhea is at best indicative and is in no way diagnostic of unilateral multiple gestation.

It is our belief that this case of unilateral tubal twin gestation represents the eighty-seventh authentically reported case in the English language journals.

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Metastatic placental tumors: Report of three cases

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THE SPREAD OF CANCER in man to distant sites is nothing new to the medical community; however, metastasis to the placenta of a gravid woman stirs the interest of most physicians. A review of the medical literature reveals only 36 such case reports which are dominated by metastatic melanoma, breast cancer, and the leukemic-lymphoma groups. The purpose of this paper is to cite three case histories with placental metastasis encountered since 1968 in the Department of Obstetrics and Gynecology at the Medical University of South Carolina.

Mrs. T., a 39-year-old black woman, gravida 10, was admitted in December, 1968, with an estimated date of confinement of January 4, 1969. She had complained of right upper-quadrant pain of a crushing quality prior to admission and had noted dark urine for three days. Her health had been good prior to this admission.

Physical examination revealed a pregnant woman who appeared chronically ill. There was no apparent icterus or edema. No significantly enlarged lymph nodes were palpable. The abdominal examination revealed a large multinodular liver below the umbilicus which was tender. The admitting diagnosis was an intrauterine pregnancy, 32 weeks' size, and metastatic carcinoma of the liver from an unknown origin.

Abnormal laboratory data consisted of only low protein of 4.0 Gm. A sulfobromophthalein revealed 73 per cent retention at 15 minutes and 52 per cent retention at 45 minutes. Chest x-ray, one-shot intravenous pyelogram, barium swallow, and mammograms were normal. A liver biopsy on December 13 revealed poorly differentiated carcinoma of unknown etiology.

On December 30, 1968, she went into spontaneous labor and was delivered of a 3 pound, 13 ounce male infant. The placenta was delivered intact with no gross abnormalities. Sections of the placenta showed the membranes and chorionic villi with scattered nodular collections of malignant epithelial cells. There was no conclusive evidence as to the primary site, although the malignancy in the placenta somewhat resembled that found in the liver biopsy. The patient's condition worsened progressively and she died on January 1, 1969. Autopsy on the patient was denied.

The infant was a premature male with moderate respiratory distress. He developed seizures, hyperbilirubinemia to 14, and hypoclacemia to 7.8 mg. per cent. Hematologic studies revealed fibrinogen of 89 mg. per cent, a prothrombin time of less than 5 per cent activity, platelet count of 216,000, and a partial thromboplastin time of 86 seconds with a control of 24 seconds. The infant demonstrated constant seizure activity and died on the tenth day after birth. An autopsy was refused.

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Mrs. V., a 44-year-old white woman, gravida 10, had an estimated date of confinement in late October, 1972. She developed symptoms in July, 1972, of acute epigastric pain radiating through to the back. Appetite decreased followed by marked nausea, vomiting, and jaundice. The physician noted an epigastric mass, hepatomegaly, and an enlarged left supraclavicular node. Biopsy of this neck mass revealed nonspecific adenocarcinoma.

Family history revealed the mother had died from leukemia, and a sister had breast cancer.

The patient was a jaundiced, depressed, and well-developed woman. The uterus was enlarged and compatible with 34 to 36 weeks' gestation. Fetal heart tones were present. The liver was palpable 4 to 5 cm. below the right costal margin.

Abnormal laboratory data included protein, 4.4; albumin, 2.1; alkaline phosphatase, 186; total bilirubin, 12 with direct bilirubin of 10.5; and serum glutamic oxalacetic transaminase, 56. The upper gastrointestinal series revealed a large epigastric mass displacing the stomach and faintly spreading the duodenal loop. On discharge, the alkaline phosphatase was 680, and the bilirubin was 30.

The patient was evaluated by the obstetric service, and believed gestation was to be approximately 35 weeks. The estimated date of confinement was near the end of October. Amniocentesis was performed and revealed lecithin/sphingomyelin ratio of 2:1. The cervix was long and closed. A cesarean section was performed on September 22, 1972, with delivery of a 6 pound, 5 ounce male fetus. The placenta weighed 550 grams and had a yellowish green tinge. Exploration of the abdomen demonstrated a large tumor of the pancreas, biopsy of which revealed an undifferentiated malignancy. Gastrojejunostomy, cholecystojejunostomy, and jejunojejunostomy were performed because of obstruction. Postoperatively, the patient healed well and was discharged.

Microscopic examination of the placenta revealed numerous foci of undifferentiated carcinoma (Fig. 1). In some areas, there was degeneration and necrosis of the chorionic villi. One ovary revealed much of its parenchyma replaced by infiltrating cords of undifferentiated carcinoma similar to that found in the placenta.

Discharge diagnosis was carcinoma of the pancreas with carcinomatosis. The patient died at a local hospital on October 31, 1972. No autopsy was performed. The child is living and well at the time of this publication.

Mrs. G., a 23-year-old white woman, gravida 2, had an estimated date of confinement of January 5, 1974. She was admitted in November, 1973. She had noted enlargement of a mole in the anterior lateral fold of the left breast approximately one year prior to admission. During the second month of gestation, a biopsy by her physician revealed a malignant melanoma. A wide in-block resection was undertaken. The patient's pregnancy continued normally until approximately two weeks prior to admission when she noted an enlarged mass in the left axilla.

Physical examination was entirely normal except for an 8 by

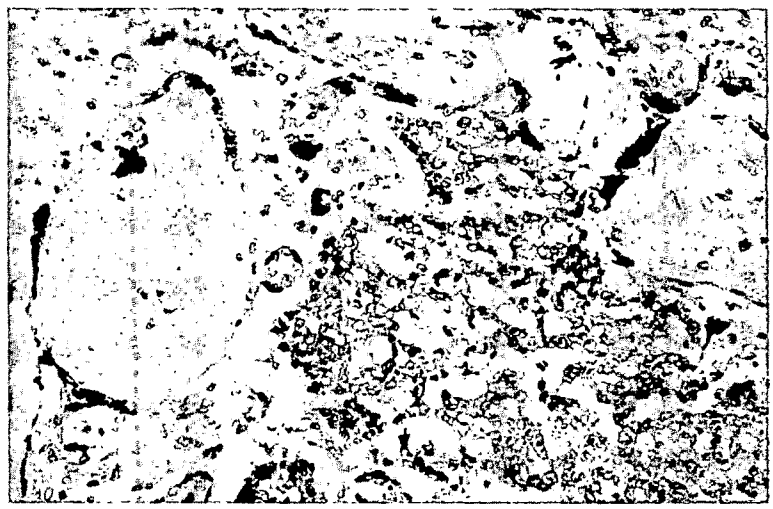


Fig. 1. Pancreatic carcinoma cells lying intervillously in the placenta.

6 by 5 cm. freely movable nontender mass in the left axilla and a palpable uterus in the abdomen consistent with an eight-month pregnancy.

Axillary node biopsy revealed metastatic carcinoma in the soft tissue consistent with malignant melanoma. Chest x-ray and intravenous pyelogram were normal. Bone scans revealed suspicious areas in the left femur, sternum, and dorsal lumbar spine. The liver scan revealed the liver to be enlarged and studded throughout with multiple areas of decreased uptake. Brain scan was normal. Urine, hemogram, Sequential Multiple Analyzer parameters of 6 and 12 were essentially normal.

She went into spontaneous labor on November 26, 1973, and was delivered of a 5 pound, 12 ounce female infant with an Apgar score of 7. The placenta appeared to be grossly normal. Microscopically, three suspicious foci of cells between the villi of the placenta were found, including cells with large nuclei, indictinct cytoplasm, and two mytotic figures within each cluster of cells. Several cells contained a granular brown pigment, which was histologically diagnosed as malignant melanoma metastatic to the placenta. Following delivery, the patient was given cyclophosphamide vincristine, 5-fluorouracil, and methotrexate. The patient died on December 16, 1973, in local hospital, and no autopsy was obtained.

A follow-up on the infant by personal communication nine months after delivery revealed the infant to be alive and doing well, progressing physically and neurologically within normal limits.

Carcinoma of the pancreas metastatis to the placenta has not been previously reported. In none of the three cases was gross tumor evident in the placenta. Two infants have progressed normally to the present date, and one died secondary to prematurity and other hematologic complications.

Rothman and associates[2] stated that half of the reported cases required routine microscopic examination to identify metastatic placental involvement. Fetal metastasis from the mother was documented in only eleven patients and this was observed in only the melanomas and leukemic-lymphoma groups.

Potter and Schoeneman[1] stated that there were 61,359,844 births in the United States in a 15-year period from 1950 to 1964. He surveyed two hospitals in Washington, D. C., and found a ratio of one cancer to 1,008 pregnancies excluding basal cell and in situ lesions. He applied this ratio to the number of births mentioned and estimated 60,872 women had concurrent cancer and pregnancy. Paradoxically, only seven reports of cancer metastasizing to the placenta or fetus were reported in the same time period, documenting a marked discrepancy between the potential for placental-fetal involvement by cancer and its reported occurrence. This discrepancy remains an enigma. The fetal and maternal circulations are separated; however, the passage of cells between the mother and fetus is known to occur. Retik and colleagues[3] have shown that tumor cells were demonstrable in pooled newborn blood of experimental animals after intravenous injection and appeared to have reached this destination without invading the trophoblast. What part fetal immunity plays remains a question. The fetus, at least in the latter half of pregnancy, is capable of reacting to maternal tumor antigens; however, many maternal cancers may be present from the time of conception and would expose the fetus when it was unable to react to foreign antigens.

Resistance to metastatic growth by the placenta was demonstrated when Pang, in 1957, and Retik, in 1962, innoculated the circulatory systems of experimental animals with cancer cells and no evidence of implants was demonstrated.

Despite its propensity to invade blood vessels, gestational choriocarcinoma, a tumor of conceptual products, has been documented to spread to the fetus in only three cases in the literature. The reverse of this situation would be metastasis of cancer from the fetus to the mother, and to our knowledge this has not been reported.

If one considers the types of cancer that occur most frequently in pregnancy, breast and cervical cancers, leukemia, and lymphoma would comprise approximately 75 per cent and melanoma would comprise only 8 per cent. Paradoxically, again, the most common tumor metastatic to the placenta is melanoma. It also would seem with the closed proximity of the cervix to the uterine corpus with their common blood and lymphatic supply there would be spread to the fetoplacental unit, but none to date has been reported.

Rothman and associates[2] suggested four maternal-fetal factors in preventing or facilitating placental-fetal involvement: (1) intervillous sequestration, (2) transvillous passage of tumor cells, (3) fetal dissemination, and (4) fetal host response. Some authors believe that the trophoblasts are a significant barrier in preventing transvillous passage of maternal tumor cells. Most tumors reported show only tumor in the intervillous space and not villous invasion.

All three cases reported here had only intervillous involvement, and, in the two infants available to follow-up, no evidence of transvillous spread or fetal involvement had occurred.

We emphasize that multiple blocks of tissue must be taken before metastatic disease can be ruled out since gross lesions may not be evident. The incidence of maternal-fetal metastasis may be higher than that cited in the literature.

We acknowledge Drs. Karen Kreutner and Oliver Williamson, fellow faculty members, for the use of their private case histories in this presentation.

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Perforated duodenal ulcer in pregnancy with double survival

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COMPLICATIONS OF peptic ulcer are rarely encountered in pregnancy, because of normal physiologic changes inherent in pregnancy itself. Diminution of gastric acidity and gastrointestinal motility alone could be responsible for amelioration of the usual symptom complex in most cases, and the occurrence of acute perforation is reported in pregnancy on only rare occasions. A review of the literature brings to light only two cases of survival of both mother and baby following acute perforation of a peptic ulcer during pregnancy. The first was reported by Lindell and Tera,[1] in 1962, and the second was reported by Winchester and Bancroft,[2] in 1966. In February, 1975, we treated a patient with the third reported case of acute perforated peptic ulcer in pregnancy with successful outcome for mother and baby.

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A 32-year-old primigravida with a 13 year history of infertility was transferred from a rural hospital on February 18, at 32 weeks' gestation, because of hypertension of 150/110, proteinuria, growth retardation, and a two-week history of nausea, vomiting, and weight loss. However, nine hours after admission, she developed sudden severe epigastric pain and hypotension of 90/50. She was moderately dehydrated; hemoglobin was 20 Gm., and hematocrit was 49 per cent. There was no history of gastrointestinal upset prior to the pregnancy, but she had had severe postprandial discomfort and epigastric pain at night since the first trimester. The fetal heart rate was normal. No contractions or hypertonus was present; the uterus was nontender, and there was no vaginal bleeding. Rebound tenderness was evident in the epigastrium.

Differential diagnosis included perforated ulcer, pancreatitis, and concealed abruptio placentae. A scout film of the abdomen showed free air under the right hemidiaphragm.

After initial resuscitation with intravenous fluids, abdominal operation revealed a large perforated duodenal ulcer. A Graham patch closure of the duodenal perforation was done. The peritoneal cavity was copiously irrigated with isotonic fluid, and the abdomen was closed without drainage.

The uterus was in keeping with approximately 28 weeks' gestation, with a few weeks' discrepancy attributed to probable dysmaturity. With this in mind, and because there had been no opportunity preoperatively for satisfactory assessment of fetal viability or possible growth retardation due to placental insufficiency, it was believed that continuation of the pregnancy offered the best hope for fetal salvage. The additional maternal risk of a combined procedure including cesarean section at the time of closure of the perforation seemed unwarranted because of lack of opportunity to stabilize the mother's condition before perforation occurred; the very small uterine size (29 cm.) was also a deterrent.

Postoperatively, the patient was given parenteral penicillin G, gentamicin, alcohol, and isoxsuprine. Hypotension led to discontinuation of isoxsuprine and alcohol, and labor ensued. Twelve hours postoperatively, a 1,500 gram female infant was delivered vaginally and transferred to the neonatal intensive care unit after simple resuscitation. The baby made slow but steady progress, eventually being discharged from the hospital on the forty-eighth day. The mother's postpartum recovery was also uneventful.

An upper gastrointestinal series prior to discharge was normal; gastric acid studies showed marked basal and stimulated elevations. Six weeks post partum, mother and baby were doing well, and no peptic ulcer symptoms were present.

Peptic ulcer in pregnancy is rare, and acute perfora-

tion occurring after viability is even rarer. Indigestion of all forms is common in pregnancy, and gastrointestinal radiography is done with reluctance. On reviewing the literature, only four cases of maternal survival following perforated ulcer were found.

It is interesting to note that in the two other cases and in our case, in which both mother and baby survived, delivery was by the vaginal route rather than by cesarean section.

The patient has had repeat acid studies, and the basal and maximal acid output are completely within normal limits. She has had no recurrence of the duodenal ulcer symptoms.

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Mechanism of suppression of gonadotropin levels in a patient with a prolactin-secreting adenoma: A longitudinal case study

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SERUM LEVELS OF follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are frequently below normal or undetectable in patients with the syndrome of galactorrhea and amenorrhea. The mechanism for the reduction in gonadotropin secretion is at present controversial. Three possible explanations are often given: encroachment of an expanding pituitary tumor on gonadotropin-secreting cells, inhibition of FSH and LH release by the direct physiologic effects of prolactin on the pituitary, or, finally, decreased secretion of both gonadotropin-releasing hormone and prolactin-inhibiting factor as a result of impeded catecholamine-mediated hypothalamic neurotransmission.[1, 2]

A patient followed longitudinally during development of a prolactin-secreting tumor provides evidence for one of these mechanisms.

The patient, a 25-year old woman, exhibited normal growth and development and experienced menarche at age 11. After several years of regular menses, she developed amenorrhea in association with galactorrhea at age 20. Clinical evaluation one year later, in 1971, revealed normal x-rays of the sella turcica. Due to the persistence of symptoms in 1972, the patient was re-evaluated, and a complete endocrinologic investigation of pituitary function was performed. Plasma prolactin titers were twentyfold elevated over normal mean levels, but growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, LH, and FSH secretions were all normal. However, 24 hour urinary excretion of estrogens was below normal. Fig. 1 shows plasma prolactin, FSH, and LH levels at 20 minute intervals over a 24 hour period during this admission. Although prolactin is clearly elevated, with a mean level of 200 ng. per milliliter, both FSH and LH show a completely normal pattern with respect to both mean levels and pulsatile secretion. There is no inverse relationship between LH and prolactin. A clomiphene-stimulation test (not shown) showed a clear response with a more than twofold increase in LH and FSH levels. No change in prolactin secretion was noticed in response to clomiphene. Three months later, ingestion of 500 mg. of L-dopa reduced the plasma prolactin concentration by 60 per cent without any change in LH secretion.

Sequential hormonal studies from May, 1973, until July 1974, are shown in Fig. 2. There was a gradual increase in prolactin levels as both LH and FSH levels were becoming markedly suppressed. During the same period, the patient had increasing complaints of headaches, and in June, 1974, it was evident from x-rays of the sella turcica that a pituitary tumor had developed (Fig. 2). At operation, a protruding soft mass was removed from the left side of the pituitary gland with a transsphenoidal approach. In tissue culture, cells from this mass released prolactin into the culture medium. Postoperatively, plasma prolactin, LH, and FSH levels returned to the normal range, and pregnancy occurred four months later. Serum prolactin levels obtained during pregnancy remained at the levels expected in normal women.

In the case reported, suppression of FSH and LH secretion correlated temporally with the gradual expansion of a prolactin-producing pituitary adenoma. Based upon this association, it is likely that the tumor compressed normal pituitary tissue and by this mechanism produced hypogonadotropism.[1] Since the hyperprolactinemia preceded the development of hypogo-

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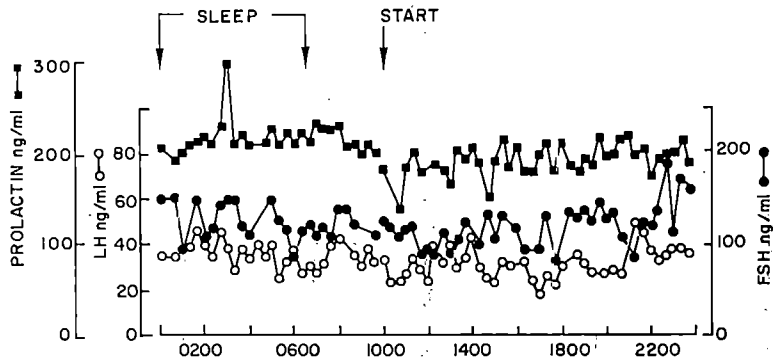


Fig. 1. LH, FSH, and prolactin levels over 24 hours in May, 1972.

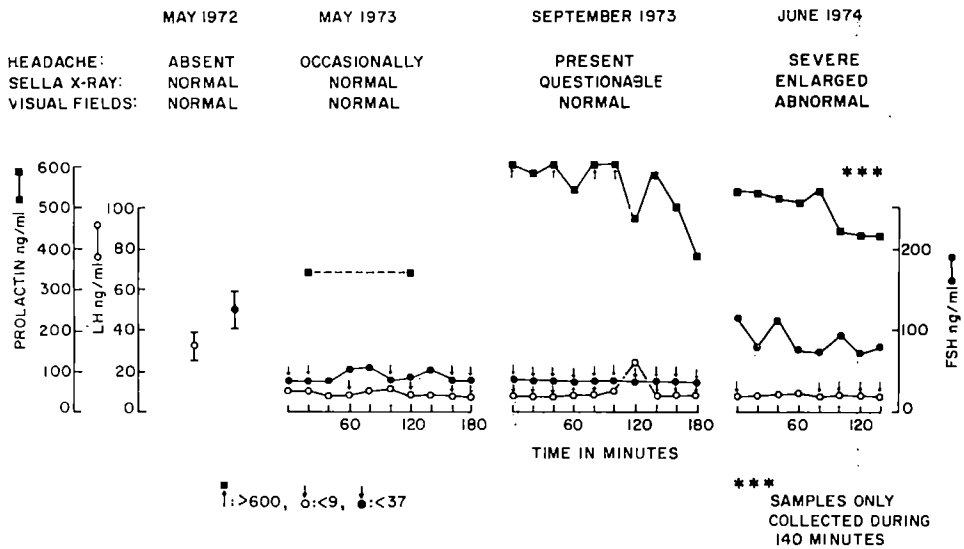


Fig. 2. Summary of longitudinal clinical and hormonal studies.

nadotropism by more than one year, direct effects of prolactin itself on gonadotropin secretion or hypothalamic dysregulation may be excluded as causes for low LH and FSH levels.[2] While the mechanism of hypogonadotropism is clearly defined in this patient, the pathophysiology of altered LH and FSH secretion in other patients with the galactorrhea-amenorrhea syndrome could be different.

The low 24 hour urinary excretion of estrogen concomitant with initially normal FSH and LH levels in this patient are of interest. This observation is consistent with the hypothesis that prolactin directly inhibits gonadotropin-mediated steroidogenesis at the ovary, as suggested by our previous studies.

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Fetal bleeding: An unusual complication of fetal monitoring

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With the advent of widespread internal fetal monitoring, reports of complications are appearing in the literature.

The following case presents a complication so far not reported.

A 19-year-old white woman, gravida 2, para 1-0-0-1 was admitted in the early hours of July 9, 1974, to the labor and delivery room at the University of Miami–Jackson Memorial Hospital. The patient was not in labor and gave a history of

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Fig. 1. Fetal side of the placenta. The clamp clearly demonstrates the tear in the fetal vessel.

membranes which ruptured spontaneously twelve hours prior to admission. Prenatal care was practically nonexisting, since she was seen only once during the month of April. At that time, physical examination was described as normal, the height of the fundus measuring 28 cm. which was consistent with the history of the last menstrual period. The past medical and family histories were entirely unremarkable. The first gestation was uncomplicated and she was delivered vaginally of a male child weighing 8 pounds, 5 ounces, two years prior to admission. Blood pressure was 110/70; pulse was 88 beats per minute; temperature was 98° F., and respirations were 20 per minute. The pertinent physical examination was limited to the abdomen and genitals. The abdomen was gravid with a fundal height of 36 cm., and the fetus was in the vertex presentation with an estimated fetal weight of 2,000 grams. The fetal heart tones were 144 beats per minute in the right lower quadrant. The pelvic examination revealed obvious leakage of clear amniotic fluid; the cervix was 4 cm. dilated and 90 per cent effaced, and the presenting part was at the −2 station. The impression on admission was a postterm gestation by dates, possible intrauterine growth retardation, and premature rupture of the membranes. Except for a hemoglobin of 9.5 Gm. and a hematocrit of 28.8 per cent, the values of all laboratory tests were within the normal range. Since the patient had membranes which ruptured more than 12 hours prior to admission, she was placed in the obstetric intensive care unit in order to start oxytocin induction of labor. Just prior to placement on the monitor,* fetal heart tones were noted to be 140 in the right lower quadrant. The intrauterine pressure catheter was then placed with the use of the semirigid guide, followed by placement of a scalp electrode. It was noted then that sustained bradycardia of approximately 90 beats per minute were present in the absence of any uterine contraction or vaginal bleeding. Attempts to correct this situation with change of position and oxygen administration were futile. The patient was then rushed to the operating room, and with general anesthesia an emergency low-segment transverse cesarean section was performed. When the uterus was entered, the amniotic cavity was noted to be filled with clots and blood. A viable female infant with an Apgar score of 3-4-6 was delivered from the right occiptotransverse position. The placenta was delivered from the anterior fundal position after oxytocin was administered. There was no evidence of uterine perforation or rupture. The maternal surface of the placenta was found to be unremarkable; however, on the fetal side, a large hematoma was noted with a tear in the fetal vessels (Fig. 1). The baby was taken to the intermediate care nursery; immediate hemoglobin and hematocrit were reported as 13.9 Gm. and 43 per cent, respectively. The infant weighed 2,040 grams, and physical and neurological examinations confirmed our impression of a pastterm baby and intrauterine growth retardation. Mother and infant subsequently had a benign course.

In our review of the literature, we found that the most consistent fetal complication has been scalp abscess and cellulitis.[1] Recently, two unusual complications have been reported, namely, leakage of cerebrospinal fluid after placement of the electrode in the anterior fontanel[2] and more recently the placement of a spiral electrode in the lower eyelid of the baby.[3] To our knowledge, no instances of fetal bleeding have been reported in the literature. The technique of insertion was reviewed with the resident. It was revealed that the catheter guide had been passed well beyond the tip of the examining fingers, above the fetal presenting part, before the catheter was inserted. Chan and associates[1] believed that this same technique was associated with the instances of uterine perforation reported by them. We also believe this was the probable etiology of our complication. Therefore, we recommend careful placement of the intrauterine catheter to ensure that the catheter guide remains below the presenting part.

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The culturability of fibroblasts from the skin of abortuses after intra-amniotic instillation of urea or prostaglandin

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Fibroblasts from fetal skin have been used extensively to confirm the prenatal genetic diagnosis work by culture of cells obtained by amniocentesis.

Park and associates[1] had successful cultures in 21 of 31 (68 per cent) samples from fetal skin of abortuses obtained from abortions induced by prostaglandin given intravenously in contrast to no successful culture in material obtained from abortions induced by intra-amniotic hypertonic saline. Recently hypertonic urea and prostaglandin have been used intra-amniotically for inducing abortions.

In this paper we will present the results of fetal skin cultures obtained after intra-amniotic instillation of urea in 25 cases and prostaglandin $F_{2\alpha}$ in 22 cases.

In urea-induced abortion,[2] 150 ml. of a urea solution containing 80 Gm. dissolved in 5 per cent dextrose and water (53 per cent) was instillated intra-amniotically after 100 to 250 ml. of amniotic fluid was removed.

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Within one hour following the urea instillation, an oxytocin solution (200 U. of oxytocin per 500 ml. of 5 per cent dextrose and 0.45 per cent sodium chloride) was given intravenously and maintained at a rate of 50 ml. per hour until approximately one hour following completion of the abortions.

In the prostaglandin $F_{2\alpha}$–induced abortions, 8 ml. of solution containing 40 mg. of prostaglandin $F_{2\alpha}$ was used intra-amniotically. If there was no response until 24 hours following the initial instillation of prostaglandin $F_{2\alpha}$, 40 mg. of prostaglandin $F_{2\alpha}$ was reinstillated intra-amniotically.

The fetuses were aborted within 48 hours after the instillations in both methods. The components of the media and the procedure of the culture were the same as those used by Park and associates.[1]

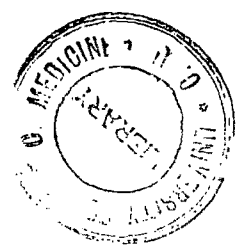
Twenty-three of the 25 specimens from the group after urea instillation failed to grow after three or four weeks in culture. Only two of the urea group showed any growth, and one of these grew only two weeks. Sixteen of 22 specimens (73 per cent) from the prostaglandin group began to grow from the third to seventh day after implantation and spread over the flask within 10 days.

The time from intra-amniotic instillation of prostaglandin to complete expulsion of the fetus does not seem to be related to the success of the cultures, but the shorter the time between expulsion of the fetus and the preparation of the culture, the greater the success obtained with the cultures.

In conclusion, whenever the fetal skin of an abortus is needed for culture, the choice of drug for inducing abortion seems to be prostaglandin $F_{2\alpha}$ infused either intravenously or intra-amniotically.

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CORRESPONDENCE

Sterilization guidelines

To the Editors:

In response to the letter of Dr. Raymond Rakow on "Sterilization guidelines" (AM. J. OBSTET. GYNECOL. 124: 215, 1976), I agree with him that irreversible surgical procedures should never be performed if reversible methods can reliably solve the existing problem. However, contraceptive tubal ligation has proved far more reliable than *any* temporary contraceptive methods for women, other than complete sexual abstinence. Women who rationally conclude they want no more children (or no children) should be afforded the means to control their own reproductive destiny with the most reliable procedure available—tubal closure.

As a psychiatrist, I seriously question Dr. Rakow's implication regarding "self-hate," "rejection of gender," and "self-mutilation" motivations of women requesting contraceptive sterilization. Thousands of unfortunate women seek this permanent contraceptive measure to avoid unwanted pregnancy which they know would mutilate their chances for healthy life adaptation and which could indeed foment self-hatred.

Dr. Rakow indicated that permanent loss of potential generativity ". . . cannot fail to reduce the human sense of self in the loser." It is possible that this idea could be tendered with regard to the male subject (although very rarely have voluntarily vasectomized men expressed regret for the operation) since his externalized genitals serve as a continual reminder of his procreative prowess. But, the female reproductive organs are internally located, and the woman differs from the man in that she does not announce her state of being every time she walks, sits, crosses her legs, and so forth. So it is quite unlikely she ruminates over a loss of procreative potential. However, should she miss her expected menstrual period, her "self-esteem" would not be elevated by fear of an unwanted pregnancy, and her "self-image" would not be enhanced by her anticipation of the ensuing complex problems—abortion versus mandatory motherhood. Her "ego identity" might become comparable to her view of a lowly breeding cow.

When Dr. Rakow drafted his letter over a year ago, he asked me to edit it for clarity and sign my approval—of its clarity—despite my opposing views. Naturally, I respect his right to express his opinions.

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Pregnancy after hemihysterectomy: Two case reports

To the Editors:

Two unusual cases in which pyohematocervix was present in one half of a double uterus were recorded by Wingfield and Roberts in 1970.[1] The present report describes two pregnancies in one of these patients and the first pregnancy of the other.

Mrs. B. F. (formerly Miss B. L.) underwent laparotomy in 1961 and 1968; at the first laparotomy, a bicornuate uterus was identified and the absence of the left kidney was confirmed, but it was not until the second laparotomy that the presence of two separate uteri and cervices with only microscopic communication between them was recognized. The left hemiuterus, including the cervix, was excised as no communication with the vagina could be demonstrated.

Mrs. B. F. was seen in the outpatient clinic after operation and remained free of the vaginal discharge and dysmenorrhea which preceded the laparotomies. She married in 1970 and presented at approximately 17 weeks' gestation in her first pregnancy. Antenatal examinations revealed no abnormality until the thirty-fifth week, when a rise in blood pressure to 135/80 mm. Hg, weight gain of 4 kilograms, and edema of both fingers and feet necessitated admission to the hospital. Symptoms subsided after 14 days of rest in bed, and she was allowed to return home. In view of the previous uterine operations and a persistent breech presentation, delivery was accomplished by elective lower uterine-segment cesarean section. Except for adhesions around the bladder which complicated its reflexion, the operation was uneventful, and a living female child, weighing 3.375 kilograms, was delivered. The right hemiuterus and its Fallopian tube and ovary appeared normal. The baby made normal progress after delivery, but Mrs. B. F. developed pyrexia which reached a maximum of 37.8° C. on the fourth postoperative day and was associated with offensive lochia, from which streptococci were isolated by culture. The pyrexia subsided rapidly after treatment with ampicillin, 250 mg. every six hours by mouth. The abdominal wound healed normally, and Mrs. B. F. was discharged from the hospital on the eleventh postoperative day. When she was seen six weeks later, the postnatal examination revealed that the uterus was involuted and the cervix appeared normal. Exfoliated cervical cells had no atypical appearance on cytologic examination.

Mrs. B. F. used the oral contraceptive pill until three months prior to her second pregnancy. Antenatal progress was again uneventful until the thirty-eighth week when, once more, she was admitted to the hospital with mild hypertension and edema of the extremities. Elective cesarean section was performed two days prior to the estimated date of confinement. Previously unsuspected twin infants were delivered. The first (male, birth weight weight 2.24 kilograms) was

delivered heard first, and second (female, birth weight 2.32 kilograms) was delivered by breech extraction. Mrs. B. F. made a straightforward postoperative recovery, and the twins progressed normally She has not reattended the hospital for postnatal examination.

Unlike Mrs. B. F., who conceived within two years of laparotomy and as soon as she married, Mrs. C. F. (formerly Miss C. M.) has experienced four years of involuntary infertility. The laparotomy performed in 1966 revealed findings very similar to those of Mrs. B. F. The left hemiuterus was distended by a pyohematocervix which failed to communicate functionally with the vagina, and the left kidney was absent. The left hemiuterus with Fallopian tube and ovary was excised.

Relief of Mrs. C. F.'s vaginal discharge and dysmenorrhea was complete following the operation, and she used the oral contraceptive pill for the first two years of marriage. Investigations were commenced after six months of involuntary infertility. Her husband's sperm count was normal (69 million per milliliter with normal morphology and motility), and basal body temperature variations indicated regular ovulation. Pain prevented introduction of the cannula into the stenosed cervix while the patient was conscious, but a hysterosalpingogram obtained with the use of general anesthesia confirmed patency of the remaining right tube and a normal outline of the uterine cavity, with allowance for its unicornuate nature. A favorable prognosis was given, and Mrs. C. F. attended the antenatal clinic in November, 1975, at 13 weeks' gestation in her first pregnancy. The uterine size corresponded to the period of amenorrhea. The pregnancy proceeded uneventfully until the thirty-second week when Mrs. C. F. was admitted to the hospital as an emergency patient. She gave a history of 21 hours' drainage of liquor amnii. The fetus was lying as an oblique breech, and the fetal heartbeat was audible. When labor became established within two hours of admission, cesarean section was performed. The uterus was moulded around the infant and appeared not to have developed sufficiently to accommodate the enlarging pregnancy. The right tube and ovary associated with the hemiuterus appeared normal. A living female infant, weighing 1.74 kilograms, was delivered by the lower-segment approach. Both mother and baby made normal progress after delivery.

Despite the close similarity of the defects of Müllerian duct fusion in these two patients, their obstetric performances have differed. Mrs. B. F. conceived readily on two occasions and her pregnancies, one of them multiple, proceeded normally to term. On the other hand, Mrs. C. F. experienced both involuntary infertility and a failure of uterine growth. A point of similarity was the malpresentation shortly before delivery which is common in association with uterine anomalies and which confirmed the intention to deliver both patients abdominally. This was, in any case, more likely in view of the possible uterine weakness resulting from operation.

I am grateful to Mr. J. G. Lawson for permission to report the further progress of these two patients, who are under his care at the University Hospital of Wales, Cardiff.

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Is there a place for the internist on the perinatal health care team?

To the Editors:

Perinatal health care currently embraces the concept of an obstetrician and pediatrician functioning as a team to provide a cosponsored type of care. Although pregnant patients frequently are followed for high-risk conditions such as diabetes mellitus, hypertension, anemia, or other medical diseases, generally accepted practice is to have the obstetrician deliver primary care with the internist available for consultation. Whether this approach to the management of high-risk pregnancy is optimal or whether the internist should become a full-fledged member of the perinatal health care team is an important issue.

I believe there is a need to change the current approach to high-risk pregnancy to allow the internist to play a more significant role in the care of these high-risk patients. A medical problem such as diabetes or hypertension often is the reason the pregnancy is considered to be high risk. The internist can bring a large clinical experience to the treatment of these diseases. However, during pregnancy, these maladies also have special features of which the internist must be aware. The obstetrician and the internist can learn from one another through a close working relationship that would be difficult to achieve through consultation notes. A close working relationship has become particularly important with the advent of improved techniques in monitoring the pregnancy. The ability to determine whether the fetus is growing optimally or when the fetus is mature enough to survive delivery has made careful control of the mother's medical problem a crucial factor in successfully managing the high-risk pregnancy.

The management of the high-risk pregnancy is no longer the role of any single physician and should be handled in regional referral centers. Any such center should include an internist as a partner in managing the patient. The internist should have special training in medical complications during pregnancy, and fellowships should be established for this purpose. Despite the team approach, pregnancy is an obstetric problem, and the obstetrician must retain ultimate responsibility for management decisions. However, within this framework, the close interchange among the obstetrician, pediatrician, and internist can only benefit the woman with a high-risk pregnancy.

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Central nervous system congenital malformations produced by narcotic analgesics

To the Editors:

Drs. Geber and Schramm's report on central nervous system (CNS) congenital malformations produced by narcotic analgesics (AM. J. OBSTET. GYNECOL. 123: 705, 1975) was very disconcerting. The lowest single doses administered produced from 0 to 6.1 per cent CNS abnormalities.

However, the lowest doses reported in milligrams per kilogram were extremely large. If one were to give comparable doses to a woman weighing 60 kilograms, one would administer, for example, 210 mg. of morphine, 762 mg. of meperidine, 166 mg. of methadone, 510 mg. of propoxyphene, or 438 mg. of codeine in a single dose. These doses certainly are not within the realm of clinical usage.

Although the researchers were attempting to discover minimal teratogenic doses, it is important to know what their experience was with clinically relevant doses of these commonly used medications. This is especially relevant in view of the implications of this paper and its last sentence: ". . . it would seem reasonable to develop both experimental animal and human clinical studies to evaluate or detect additional heretofore unsuspected correlations between fetal exposure to narcotic analgesics and postpartum growth and development deficits."

Perhaps in the future alarming reports such as this, dealing with very commonly used medications, could be followed by a commentator review in the JOURNAL. This report, misconstrued by the lay press, certainly could cause considerable difficulties for any practicing obstetrician.

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Reply to Dr. Santomauro

To the Editors:

I am sure Dr. Santomauro is not alone in his reaction to the report concerning narcotic analgesics and congenital malformations in animals. Just as certain is the possibility that the lay press will manipulate the data and words so that a number of patients will cause some difficulties for some obstetricians. This is the natural history of any report that deals with a drug or any substance that is clinically popular or commonly used by the lay public. I believe Dr. Santomauro must have encountered this problem repetitively with cigarettes and alcohol in his patients. Both the research and clinical reports on these two substances are now rather clear in establishing their primary role as potent factors involved in the induction of numerous prepartum and postpartum problems in the child. In addition, aspirin, some anticonvulsants used for the control of epilepsy, some minor tranquilizers, some vitamins, some antibiotics, and some inhalation general anesthetics, to name just a very few of the commonly prescribed compounds now being recognized as potentially teratogenic in human subjects, are going to pose further difficulties for the obstetrician in the coming years. This expanding list of potential and proved teratogens in human subjects is predictable, I believe, from the animal research investigations which described the problem for each of the substances years in advance of the present retrospective recognition of the correlation between the clinical use of the compounds and congenital anomalies. In general, animal research models have utilized significantly higher doses of the compound being evaluated than the doses utilized clinically, and for this reason the data were either ignored or dismissed with the statement, "Any substance will do something if you give enough of it." I am not sure that statement is true, but I do know it is misleading. More correctly stated, most substances will exhibit a dose-response relationship when evaluated in a wide variety of test situations.

Critics of the results often tend to forget or ignore the lower end of the test data and concentrate on the upper dose limits utilized by the investigation to obtain the total number of biological parameters that can be shown only if higher doses are included in the dosage schedule. Even the lower end of the dose-response curve often is considered beyond useful comparison to human exposure levels. However, it is well established that rodents, and many other test animals, live physiologically and metabolize many substances at biological rates several quantitative magnitudes different from those of human subjects. The qualitative differences between rodents and human subjects is much less and sometimes nonexistent. Also, it has been demonstrated by several investigators that the known human teratogens can be predicted as those which have an animal teratogenic dose one tenth or less of the dose lethal to the animal mother. On the basis just described, our data would indicate codeine, pentazocine, propoxyphene, methadone, and meperidine should be closely monitored in retrospective studies to determine any possible implication in the genesis of human anomalies. Hydromorphone would appear to be a borderline compound, but it is still within the range of concern. Finally, it must be kept in mind that any single compound studied in animals is not to be considered as having the exact same effect in the human subject. The animal lives in a controlled environment with a relatively balanced diet available. The pregnant animal is not subjected to the many additional potentially teratogenic situations and substances the human subject is routinely exposed to throughout daily living. Animal studies have shown conclusively that summation and potentiation between various classes of

teratogenic substances and factors can and do occur. This situation, in all probability, should be considered to be operative in the human subject as well.

All new drugs and substances being approved for human use are *now* being screened by a very extensive series of tests for both short- and long-term reproductive effects. This was not the case when many of the commonly used narcotic analgesics were originally studied. The same is true for the majority of the "older" officially approved drugs available. This situation is now being investigated, and initial studies by the Food and Drug Administration are starting the long process of updating reproductive safety data. Finally, it should be emphasized that the investigation was not designed to eliminate the use of the various compounds but to call attention to *possible* risks involved in their use during critical periods of fetal organogenesis. The individual physician must be the final judge to balance risk versus need. In making the critical clinical decisions, all possible facts should be available.

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Obstetrics and Gynecology Review Course

The "Obstetrics and Gynecology Review Course" will be held October 2-10, 1976, at the Royal Biscayne Beach Hotel and Racquet Club, Key Biscayne, Florida. It is designed for obstetricians and gynecologists who are preparing for certification examinations or who wish to be brought up to date in all aspects of obstetrics and gynecology. The course will be credited in American Medical Association Category 1 for 53 hours minimum and 69 hours maximum. The Program Director is William Little, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of Miami School of Medicine. For further information, contact: Division of Continuing Medical Education, University of Miami School of Medicine, P. O. Box 520875, Miami, Florida 33152. Telephone: (305) 547-6716.

BOOKS

Books received

Clinical Aspects of the Tetratogenicity of Drugs. Hideo Nishimura and Takashi Tanimura. 453 pages, illustrated. New York, 1975, American Elsevier Publishing Company, Inc. $53.95.

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Gynaecological Pathology. M. Haines and Claude Taylor. 552 pages, illustrated. New York, 1975, J. & A. Churchill, Ltd. $40.00.

Gynecology and Obstetrics: The Health Care of Women. Seymour L. Romney, Mary Jane Gray, A. Brian Little, James A. Merrill, E. J. Quilligan, and Richard Stander. 1163 pages, illustrated. New York, 1975, McGraw-Hill Book Company, Inc. $29.50.

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The Physiology of the Newborn Infant. Ed. 4. Clement A. Smith and Nicholas M. Nelson. 771 pages, illustrated. Springfield, Illinois, 1976, Charles C Thomas, Publisher. $52.00.

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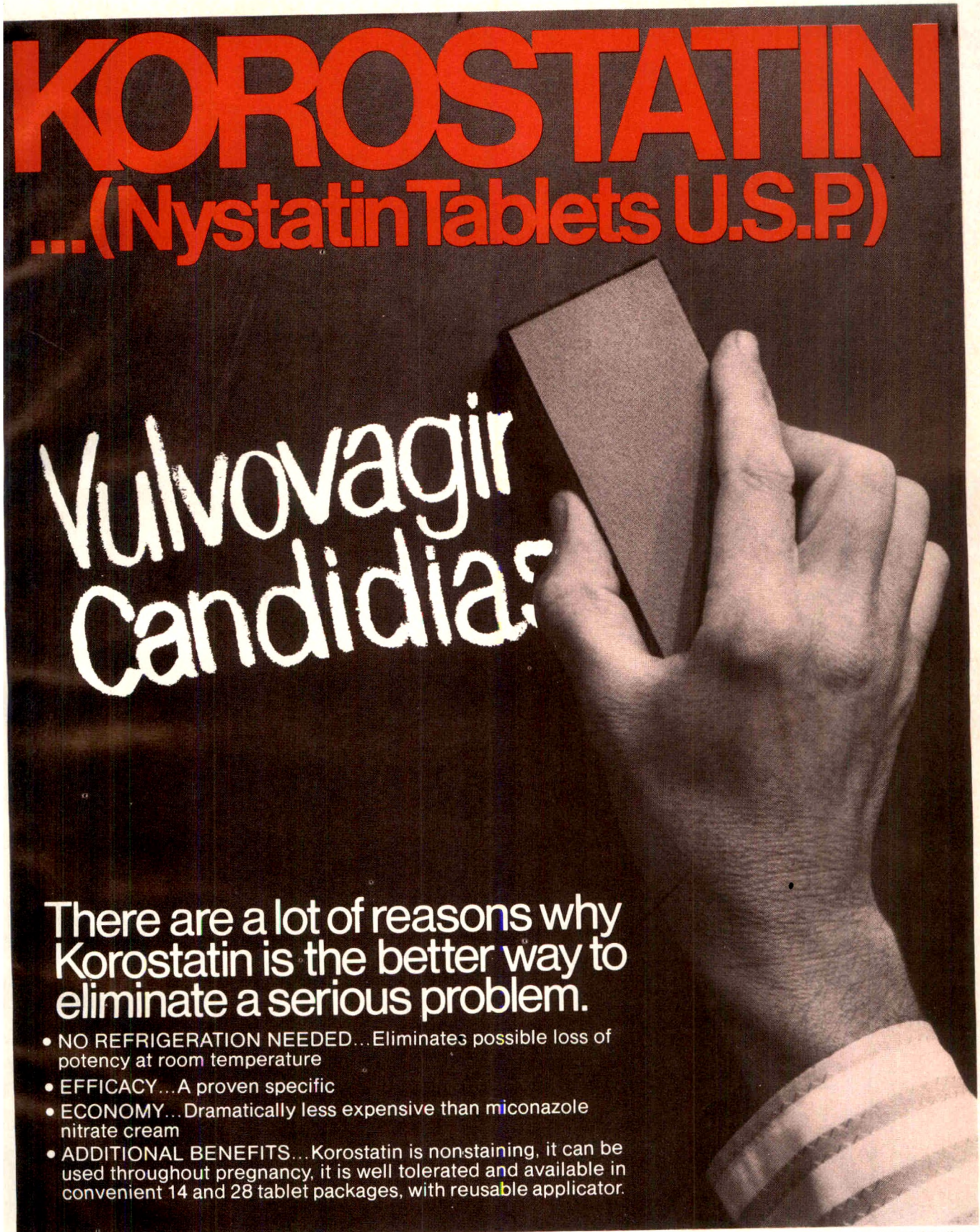
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INDICATIONS FOR USE: KOROSTATIN (Nystatin) Vaginal Tablets U.S.P. are indicated in the local treatment of vulvovaginal candidiasis.

CONTRAINDICATIONS: All Nystatin preparations are contraindicated in patients with a history of hyper-sensitivity to Nystatin.

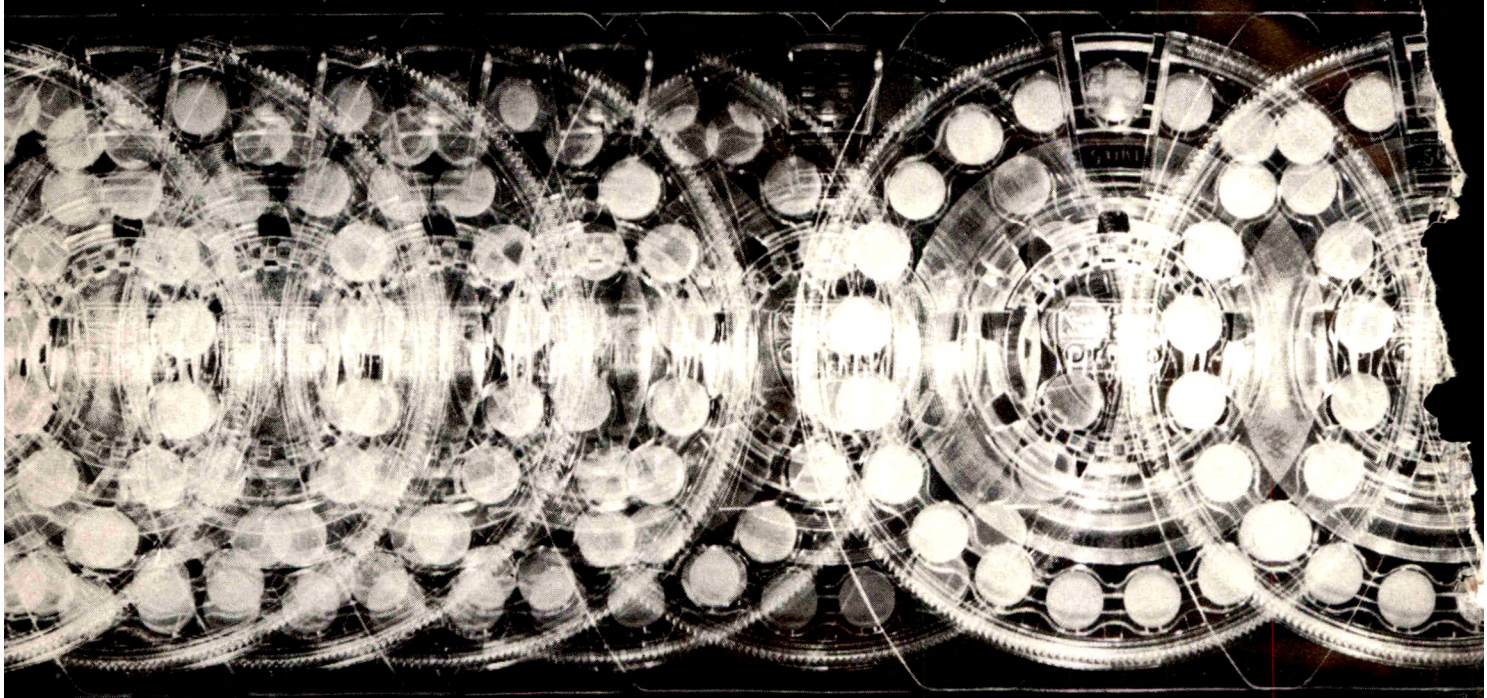
ADVERSE REACTIONS: Nystatin, U.S.P. is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even on prolonged administration. If irritation during intravaginal use should occur, discontinue the medication.

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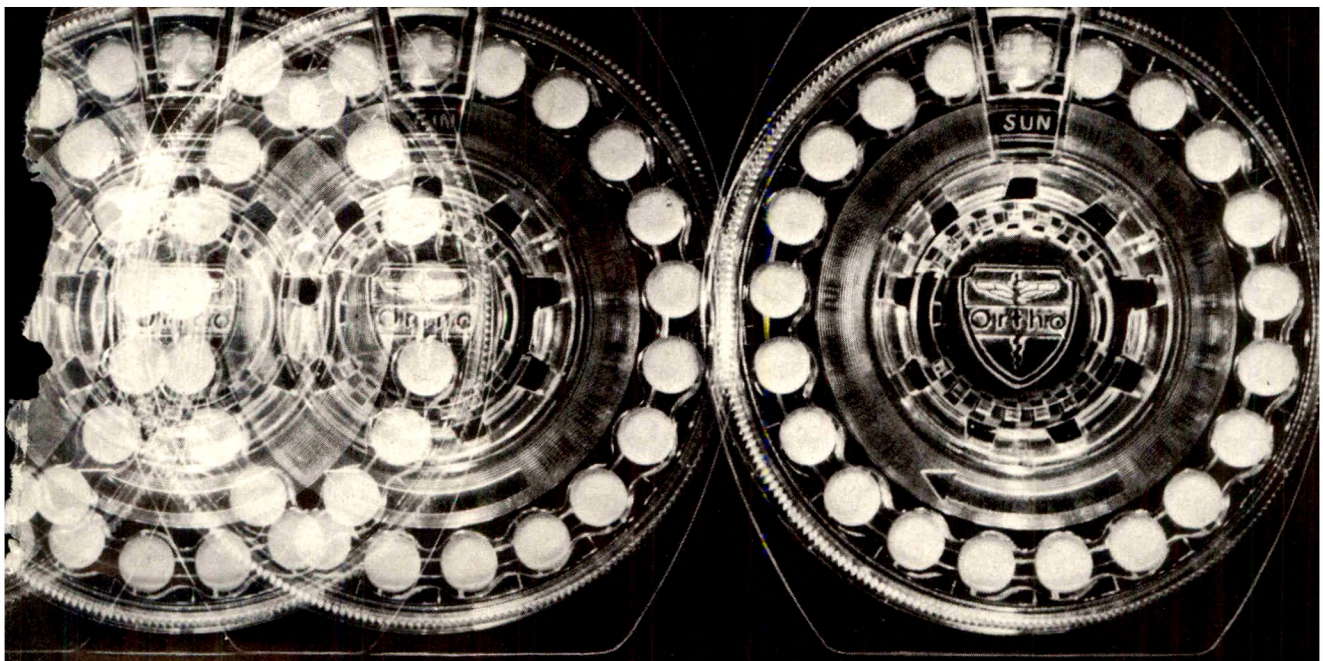


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In the 28-day regimen, each green tablet contains inert ingredients.

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Reformulated without dye *ModiCon is back, but without the coloring agent. Quality control testing on new white ModiCon demonstrates excellent stability.*

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Two regimens *Available in both 21 and 28-day regimens.*

†It should be noted that pregnancy rates are usually derived from studies conducted by different investigators in several population groups and they cannot be compared with precision.

‡Serious as well as minor side effects have been reported following the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

ModiCon TRADEMARK is back.

Each white tablet contains 0.5 mg norethindrone and 0.035 mg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.



In both 21 and 28-day regimens

Description: Each MODICON Tablet contains 0.5 mg of the progestational substance, norethindrone, together with 0.035 mg of the estrogenic compound, ethinyl estradiol.

Each green tablet in the 28-day regimen contains inert ingredients.

Actions: MODICON acts through the mechanism of gonadotrophin suppression, i.e., through the estrogenic and progestational actions of the ingredients. Alterations in cervical mucus and in the endometrium may also contribute to the efficacy of MODICON.

Special note: Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

The dropout rate for medical reasons, as observed in the clinical trials conducted with MODICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug.

The physician should consider a thorough discussion with each patient about the prescribing information, risks and benefits associated with oral contraceptives, taking into account various factors such as age and other physical conditions.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure and reduced tolerance to carbohydrates, have been reported and appropriate tests should be conducted to monitor these during oral contraceptive therapy. Liver disease has also been reported, and the physician should be alert to its earliest manifestations.

Long-term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

Indication: Contraception.

Contraindications: 1. Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction, or a past history of these conditions. 2. Markedly impaired liver function. 3. Known or suspected carcinoma of the breast. 4. Known or suspected estrogen-dependent neoplasia. 5. Undiagnosed abnormal genital bleeding. 6. Known or suspected pregnancy.

Warnings: 1. The physician should be alert to the earliest manifestations of thrombotic and thromboembolic disorders, thrombophlebitis, cerebrovascular disorders including hemorrhage, pulmonary embolism and retinal thrombosis. Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism and cerebral vascular disease, occlusive or hemorrhagic, and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to these conclusions and three in this country.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold while the United States studies found relative risks of 4.4 to 11, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers.

In May 1974, the Royal College of General Practitioners in England[8] issued an interim report of its continuing large-scale prospective study comparing a user group to a nonuser group. This study in its interim analysis states, "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." The study also reported a higher incidence of superficial and deep vein thrombosis in users as compared to nonusers. The risk of superficial and deep vein thrombosis was reported to be lower in women using 50 mcg estrogen preparations.

The Sartwell study[4] indicated that the risk did not persist after discontinuation of administration. Both the Sartwell and the Royal College studies indicated that the degree of risk was not associated with duration of treatment.

In a collaborative American study[5,6] of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of thrombotic stroke was 4.1 to 9.5 times greater in users than in nonusers. A comparable estimate for hemorrhagic stroke was 2.0.

None of the American studies was designed to evaluate a difference between products. However, the Sartwell study[4] suggested that there might be an increased risk of thromboembolic disease in users of sequential products.

Other retrospective studies[9,10] have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. It has been recommended that therapy be discontinued at least one month prior to elective surgery.

In May of 1975 two separate retrospective case control studies relating to fatal and nonfatal myocardial infarction in users and nonusers of oral contraceptives were reported.[11,12] The studies estimate that the increased risk of hospital admission for myocardial infarction associated with the use of oral contraceptives as compared to nonusers is 2.7 times in the 30-39 age group and 5.7 times in the 40-44 age group; and the risk of death associated with the use of oral contraceptives as compared to nonusers was increased 2.8 times for users in the 30-39 age group and 4.7 times in the 40-44 age group. One of these studies reported that oral contraceptive users who had myocardial infarction were more likely to be heavy smokers and have certain additional risk factors, i.e., treated hypertension and diabetes, pre-eclamptic toxemia, obesity and type II hyperlipoproteinemia.

2. Discontinue oral contraceptive medication if there is: gradual or sudden partial or complete loss of vision; proptosis or diplopia; onset or aggravation of migraine or development of headache of a new pattern which is recurrent, persistent or severe; papilledema; or any evidence of retinal vascular lesions.

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy.[13,14] The safety of MODICON in pregnancy has not been demonstrated. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

5. Hepatic lesions (adenomas, hepatomas, hamartomas, regenerating nodules, etc.), occasionally fatal, have been reported in women on oral contraceptives. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen. These lesions should be considered if the patient has abdominal pain or evidence of intra-abdominal bleeding. This has been reported in short-term as well as long-term users of oral contraceptives.

Precautions: 1. A thorough history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration and should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals. 2. Endocrine and possibly liver function tests may be affected by treatment with MODICON. Therefore, if such tests are abnormal in a patient taking MODICON, it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated. 6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 7. Any possible influence of prolonged MODICON therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving MODICON therapy. 9. The age of the patient constitutes no absolute limiting factor, although treatment with MODICON may mask the onset of the climacteric. 10. The pathologist should be advised of MODICON therapy when relevant specimens are submitted. 11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steriods. 12. Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, MODICON should be discontinued. This condition is more likely to occur in patients who have experienced cholestatic jaundice of pregnancy. Patients with a history of cholestatic jaundice of pregnancy should be carefully observed during MODICON therapy.

Adverse reactions observed in patients receiving oral contraceptives: A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism, cerebral thrombosis and hemorrhage, myocardial infarction, gallbladder disease.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; hepatic lesions with or without intra-abdominal bleeding.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, which may persist, cholestatic jaundice, migraine, rash (allergic), mental depression, change in weight (increase or decrease), breast changes (tenderness, enlargement and secretion), changes in cervical erosion and cervical secretions, suppression of lactation when given immediately postpartum, rise in blood pressure in susceptible individuals.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post-treatment, which tends to occur more frequently in women with a history of menstrual disorders, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, intolerance to contact lenses, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruptions, itching, vaginitis.

The following laboratory results may be altered by the use of oral contraceptives: hepatic function—increased sulfobromophthalein retention and other tests; coagulation tests—increase in prothrombin, Factors VII, VIII, IX and X; decrease in anti-thrombin III; increase in platelet aggregability; thyroid function—increase in PBI, and butanol extractable protein-bound iodine and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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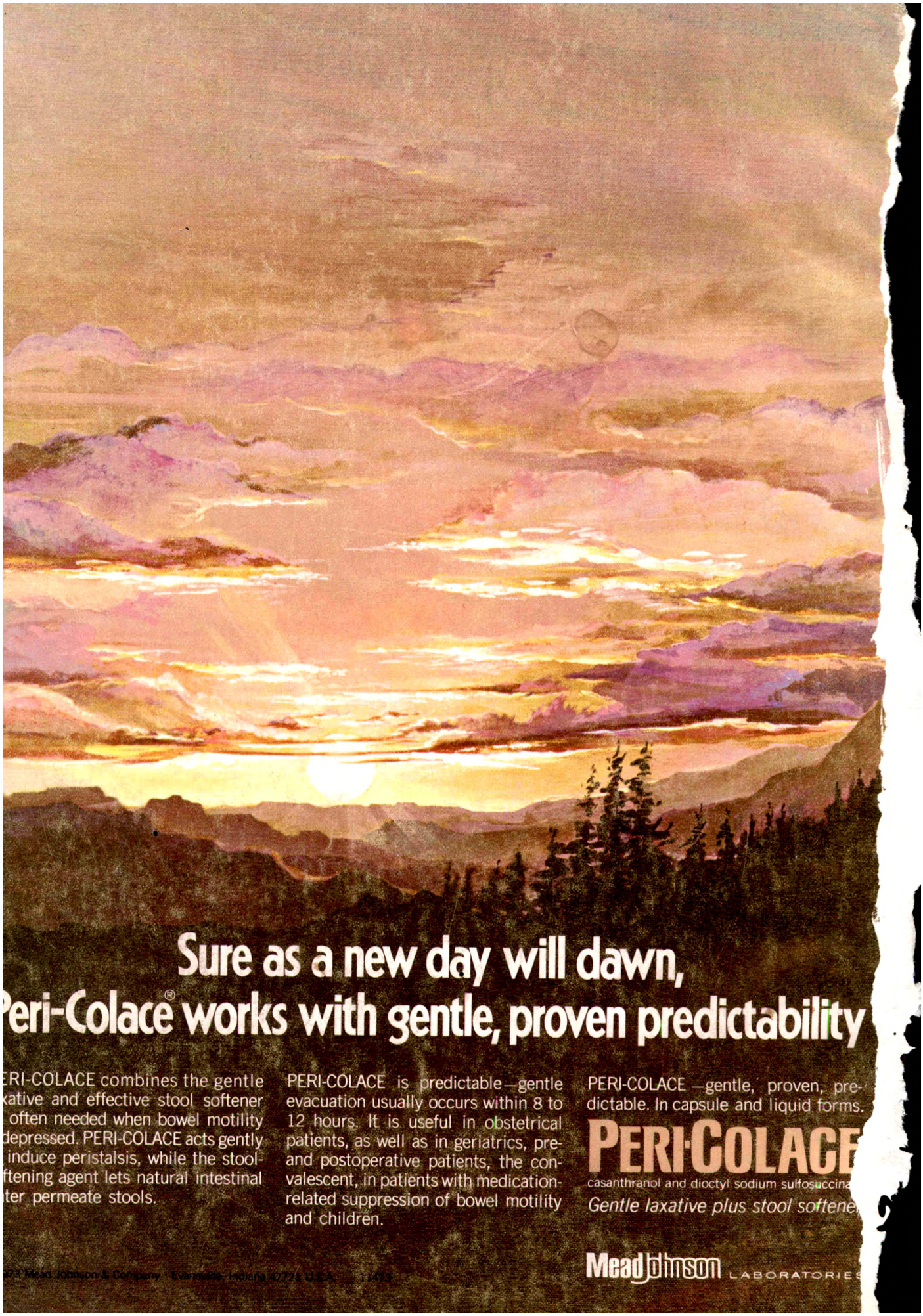
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